federal register

MONDAY, JULY 11, 1977

PART III

ENVIRONMENTAL PROTECTION AGENCY

■

DRINKING WATER AND HEALTH

Recommendations of the National Academy of Sciences

ENVIRONMENTAL PROTECTION AGENCY

[FRL 756-4]

DRINKING WATER AND HEALTH

Recommendations of the National Academy of Sciences

This publication of the recommendations of the National Academy of Sciences (NAS) is made according to the requirements of the Safe Drinking Water Act (Pub. L. 93-523).

The present publication consists essentially of the summary of the NAS report which was delivered to Congress on May 26, 1977. The full report was delivered on June 20, 1977.

The Safe Drinking Water Act (Pub. L. 93-523) was enacted on December 16, 1974, giving the Administrator of the Environmental Protection Agency (EPA) the power to control the quality of the drinking water in public water systems through regulation and other means. The Act called for a three-stage mechanism for the establishment of comprehensive regulations for drinking water quality:

1. Promulgation of National Interim Primary Drinking Water Regulations.

2. A study to be conducted by the National Academy of Sciences, within 2 years of enactment, on the human health effects of exposure to contaminants in drinking water, and

3. Promulgation of Revised National Primary Drinking Water Regulations based upon the NAS report.

National Interim Primary Drinking Water Regulations, pursuant to section 1412(a) of the Act, were promulgated on December 24, 1975, and July 9, 1976, to become effective on June 24, 1977. These were based on the Public Health Service Drinking Water Standards of 1962, as revised by the EPA Advisory Committee on the Revision and Application of the Drinking Water Standards, and contain maximum contaminant levels and monitoring requirements for microbiological contaminants, 10 inorganic chemicals, 6 organic chemicals, radionuclides and tuebidity.

Section 1412(b)(1)(A) of the Act States:

> Within 10 days of the date the report of the study conducted pursuant to subsection (e) is submitted to Congress, the Administrator shall publish in the FEDERAL REGISTER, and provide opportunity for comment on, the—
>
> (i) Proposals in the report for recommended maximum contaminant levels for national primary drinking water regulations, and
>
> (ii) List in the report of contaminants the levels of which cannot be determined but which may have an adverse effect on the health of persons.

In essence, the report of the National Academy of Sciences study should provide health goals for contaminants in drinking water, i.e., levels at which there are no known adverse health effects. The Administrator must then, using the information supplied by the National Academy of Sciences, develop maximum contaminant levels (MCL's) for National Primary Drinking Water Regulations or treatment requirements. In doing so, the Administrator may modify the recommendations of the Academy by incorporating safety factors, by taking economics into account, or for other reasons. The basis for the Administrator's actions will be adequately explained in drinking water regulations subsequently published.

Based on the completed National Academy of Sciences Report and the findings of the Administrator, EPA will publish:

(1) Recommended Maximum Contaminant Levels (health goals) for substances in drinking water which may have adverse effects on humans. These recommended levels will be selected so that no known or anticipated adverse effects would occur, allowing an adequate margin of safety. A list of contaminants which may have adverse effects, but which cannot be accurately measured in water, will also be published.

(2) Revised National Primary Drinking Water Regulations. These will specify MCL's or require the use of treatment techniques. MCL's will be as close to the recommended levels for each contaminant as is feasible. Required treatment techniques for those substances which cannot be measured will reduce their concentrations to a level as close to the recommended level as is feasible. Feasibility is defined in the Act as use of the best technology, treatment techniques and other means which the Administrator finds are generally available (taking costs into consideration).

The recommendations of the National Academy of Sciences follow. The report is prefaced with an explanation of the Academy's interpretation of their responsibilities under the Safe Drinking Water Act, and an outline of the type of recommendations the Academy was able to furnish. The report, entitled "Drinking Water and Health," is a summary of the full report of the Academy's study of contaminants in drinking water. Copies of this summary report are available from the Criteria and Standards Division, Office of Water Supply (WH-550), Environmental Protection Agency, Washington, D.C. 20460. The Academy has scheduled a public meeting July 7, 1977 at 9:00 AM at 2101 Constitution Avenue NW, Washington, D.C. 20418, to discuss the content of the full report.

Copies of the prepublication draft of the full report are available for inspection at the Academy and EPA Headquarters. Telephone 202-755-5643 for additional information.

The public is invited to comment in writing on the Academy's recommendations. All communications should be sent to Dr. Joseph A. Cotruvo, Director, Criteria and Standards Division, Office of Water Supply (WH-550), Environmental Protection Agency, Washington, D.C. 20460. Comments should be received by August 31, 1977, but comments received after that date will be considered as time permits.

Dated: June 30, 1977.

BARBARA BLUM,
Acting Administrator.

THE NATIONAL ACADEMY OF SCIENCES STUDY

LEGISLATION AND TERMS OF REFERENCE OF THE STUDY

The Safe Drinking Water Act of 1974 and the NAS study (Pub. L. 93-523)

PURPOSE OF LEGISLATION

The purpose of the legislation is to assure that the public is provided with an adequate quantity of safe drinking water. It is to assure that water supply systems serving the public meet minimum national standards for protection of public health.

Until passage of the Act, the Federal Government was authorized to prescribe drinking water standards only for water supplies used by interstate carriers, and they were enforceable only with respect to contaminants capable of causing communicable diseases. Pub. L. 93-523 authorized the Environmental Protection Agency to establish Federal standards for protection from all harmful contaminants and established a joint Federal-State system for assuring compliance with these standards and for protecting underground sources of drinking water.

ABRIDGED SUMMARY OF THE LEGISLATION

a. Required the Administrator of EPA to prescribe national drinking water regulations for contaminants which may adversely affect health.

b. *Provided*, That such regulations apply to public water systems and protect health to the maximum extent feasible.

c. *Provided*, That interim primary regulations be prescribed initially and that, after a study by the National Academy of Sciences, health goals were to be established and revised primary regulations promulgated. That portion of the Act pertaining to the NAS study and the scope of work is detailed below.

d. Provided for a number of other requirements and administrative authorizations not directly related to the NAS study.

NEED FOR LEGISLATION

Congressional hearings, EPA studies, and evidence from a number of sources established that legislative authority prior to passage of the Act was inadequate to assure that water supplied to the public was safe to drink.

This conclusion was based on evidence that waterborne disease outbreaks still occur in this country. Examples include an epidemic at Riverside, California in 1965 that affected 18,000 people, an outbreak of gastroenteritis in Angola, New York in 1968 affecting 30 percent of the population and an epidemic of giardiasis in Rome, New York in 1974 affecting almost 5,000 people. According to a 1970 EPA survey of 969 drinking water supply systems, approximately 8 million people in this country are served water that is potentially dangerous in that it failed to meet the mandatory standards set by the Federal Government with respect to interstate carrier systems. The deficiencies in the majority of cases were in smaller systems.

Until passage of the Act there was no provision in Federal law to protect the public from chemical poisoning and none to protect those not traveling on interstate conveyances from being supplied with drinking water which may cause communicable or noncommunicable illness.

Several extensive surveys have shown serious deficiencies in the number of water samples examined and in the bacteriological and chemical quality of drinking water. Many systems had physical deficiencies including poorly protected groundwater sources, inadequate disinfection and clarification capacity. In addition, plant operators were inadequately trained. Plants were not

being inspected by State or local authorities. In one survey, 50 percent of plant officials did not remember when, if ever, they had been surveyed by a State or local health department.

House of Representatives Report No. 93–1185 and Senate Report No. 93–231 and Pub. L. 93–523 are the sources of information for the foregoing.

Pub. L. 93–523 (section 1412(e)) mandated the NAS study as follows:

1. The Administrator shall enter into appropriate arrangements with the National Academy of Sciences (or with another independent scientific organization if appropriate arrangements cannot be made with such Academy) to conduct a study to determine:

A. The maximum contaminant levels which should be recommended in order to protect the health of persons from any known or anticipated adverse effects, and

B. The existence of any contaminants the levels of which in drinking water cannot be determined but which may have an adverse effect on the health of persons.

2. The result of the study shall be reported to Congress no later than 2 years after the date of enactment of this title. The report shall contain:

A. A summary and evaluation of relevant publications and unpublished studies;

B. A statement of methodologies and assumptions for estimating the levels at which adverse health effects may occur;

C. A statement of methodologies and assumptions for estimating the margin of safety which should be incorporated in the national primary drinking water regulations;

D. Proposals for recommended maximum contaminant levels for national primary drinking water regulations;

E. A list of contaminants the level of which in drinking water cannot be determined but which may have an adverse effect on the health of persons; and

F. Recommended studies and test protocols for future research on the health effects of drinking water contaminants, including a list of the major research priorities and estimated costs necessary to conduct such priority research.

3. In developing its proopsals for recommended maximum contaminants levels, the National Academy of Sciences shall evaluate and explain the impact of the following considerations:

A. The existence of groups or individuals in the population which are more susceptible to adverse effects than the normal healthy adult.

B. The exposure to contaminants in other media than drinking water (including exposures in food, in the ambient air, and in occupational settings) and the resulting body burden of contaminants.

C. Synergistic effects resulting from exposure to or interaction by two or more contaminants.

D. The contaminant exposure and body burden levels which alter physiological function or structure in a manner reasonably suspected of increasing the risk of illness.

4. In making the study under this subsection, the National Academy of Sciences (or other organization) shall collect and correlate:

A. Morbidity and mortality data and

B. Monitored data on the quality of drinking water. Any conclusions based on such correlation shall be included in the report of the study.

5. Neither the report of the study under this subsection nor any draft of such report shall be submitted to the Office of Management and Budget or to any other Federal agency (other than the Environmental Protection Agency) prior to its submission to Congress.

6. Of the funds authorized to be appropriated to the Administrator by this title, such amounts as may be required shall be available to carry out the study and take the report.

SCOPE OF WORK

The Academy will undertake to complete the study and report described in section 1412(e) of the Public Health Service Act, as amended by the Safe Drinking Water Act, with the following understanding: The Academy considers that the intent of Congress in using the phrase "maximum contaminant levels which should be recommended * * * in order to protect the health of persons from any known or anticipated adverse effects" is to provide for recommendations that are consistent with the best scientific knowledge. It is the Academy's judgment that from a scientific point of view, the absolute guarantee of safety implied by this language cannot be made for most or all of the contaminants to be studied. The Academy report will explain and discuss this point. Accordingly, with respect to recommended levels, taking only health effects into account, the Academy's report will provide the following:

(1) Where there are sufficient data from which a human dose-response relationship can be projected with some degree of precision, a projection will be made. The projection will be explained and its qualifications will be made explicit.

(2) For contaminants for which the data are of sufficient quantity and quality, the Academy will exercise its scientific judgement and identify and propose contaminant levels for which it anticipates the risk of adverse health effects to be specifiable and very small. The risks at the proposed levels will be described, with an explanation as to why no "safe" level has been identified.

(3) For contaminants for which the evidence provides no scientific basis or methodology for recommending levels, the Academy will describe the available data, and its significance in terms of known or anticipated adverse health effects.

Thus further definition of the scope of work was developed jointly between NAS and EPA.

Summary Report: Drinking Water and Health

INTRODUCTION

The high quality of drinking water in the United States is recognized throughout the world, and popularly endorsed by the freedom with which water is consumed. Nevertheless, mounting concern over the spread of environmental pollution and the application of increasingly sensitive methods of analysis have led to new legislation that seeks to ensure that the quality of drinking water poses no threat to public health.

The Safe Drinking Water Act of 1974 (Pub. L. 93–523) requires the Administrator of the Environmental Protection Agency (EPA) to promulgate national standards for the purity of drinking water and regulations for enforcing them. The Act also directs the Administrator to arrange with the National Academy of Sciences, or other appropriate organization, to study the adverse effects on health attributable to contaminants in drinking water. This report summarizes the result of that study. A précis of the legislation and its background, the objectives of the study, and the names of those who contributed to it are given in the Appendixes.

The primary purpose of the study has been to assess the significance of the adverse effects that the constituents of drinking water may have on public health. The economic or technological feasibility of controlling the concentration of these constituents is outside the scope of the study. The health effects associated with some methods of disinfection have received attention, but the relative effectiveness and potential hazards associated with the various methods of water disinfection have not been evaluated.

Application of analytical methods of great sensitivity has, in recent years, expanded our knowledge of the occurrence and diversity of impurities in drinking water. However, information about the results of chronic ingestion, at low dose rates, of most of these substances is acquired slowly because the bioassays that are usually required may take two or more years to complete. Although new approaches to the problem of estimating chronic adverse health effects may, in the future, ease this difficulty, the current knowledge on which this study is based is insufficient to assess all the contaminants of drinking water. The results reported here must therefore be considered as the first contribution of an effort that should be continued.

GENERAL CONSIDERATIONS

Besides the known constituents of water, we have considered also some that it would be plausible to expect to be present, even though they have not yet been identified. (Certain pesticides used in large quantities fall into this category.)

In our review of water constituents, we have attempted to take into account not only their identities, concentrations, and toxicities, but also have considered other questions, such as:

1. What reason is there for concern about the material? What risks are associated with its presence in water?
2. How does the material get into water?
3. What sources are there other than water?
4. What contaminants need to be controlled?
5. Are there special places or persons at higher than average risk?
6. Are there essential health requirements for this material? (See particularly the discussion of inorganic solutes.)
7. In view of the data at hand, can one say that this is a material that causes temporary ill effects? permanent ill effects? reversible effects?
8. In view of these effects—and their reversibility (or lack of it)—is it possible to set "no-observed-adverse-health-effects" levels?
9. For materials with special health benefits, what concentrations will maximize these benefits, while keeping the health risk, associated with them at an acceptably low level?
10. What additional information is required to resolve the outstanding problems?

Many of the constituents of drinking water occur naturally, and enter water from the rocks and the soil and the air. Some are the natural waste products of men or animals. Others are artificial or synthetic materials, made and used for special purposes, that inadvertently find their way into water. Yet others occur naturally, but have become more widely distributed in populated areas as a result of industrial and agricultural activity.

WATER CONSUMPTION

In this study, the average amount of water consumed per person is assumed to be two liters per day. This is also the amount used by the EPA to calculate the current interim standards. Daily consumption of water is a function of temperature, humidity, physical activity, and other factors that vary widely. Although average water consumption per capita may be estimated from the literature on human physiology and nutrition to be

about 1.6 liters/day, the larger volume of 2 liters/day was adopted as representing the intake of the majority of water consumers. We estimate that most of those who consume volumes larger than 2 liters/day still are afforded adequate protection because the margin of safety estimated for the contaminants is sufficient to offset the increased water consumption. Nevertheless, consideration should be given to establishing some standards on a regional or occupational basis to take extremes of water consumption into account.

SPECIAL CASES

Groups of people who may be more susceptible than average for the whole population are considered in connection with the particular contaminants to which they are sensitive.

This report is concerned only with water that is used for drinking. Although all contaminants may cause problems when present in water used in health care facilities, the health hazards associated with such diverse uses of water as in humidifiers, kidney dialysis units, laundries, heating and cooling equipment, or many special uses that require further treatment of tap water, have not been considered.

FINDINGS OF THE STUDY

SAFETY AND EXTRAPOLATION

The hazards of ingesting chemical pollutants in drinking water can be assessed in two general ways: With epidemiological studies and with laboratory studies of toxicity. The aim of both types is to provide information on the risk to man.

Most of the current knowledge of toxicity is based on observations of the effects on man and animals of doses and dose rates that are much larger than those that correspond to the usual concentrations of harmful materials in drinking water. There is, consequently, great uncertainty in estimating the magnitude of the risk to health that ingestion of contaminants in water may produce. An additional problem is presented by the combined effects of two or more contaminants.

The theoretical and experimental bases for extrapolating estimations of risk to low levels of dose have been reviewed. Some principles are proposed to guide the conduct of this and similar studies.

Large populations are exposed repeatedly, over long periods of time, to minute amounts of potentially toxic contaminants in drinking water. Delayed, essentially irreversible, effects can occur. Methods and criteria of classical conventional toxicology do not always provide reliable means for assessing long-term toxic effects such as carcinogenesis. Extrapolation from animal data to man is uncertain; hence, novel considerations have to be applied to assess risk.

The insidious effects of chronic exposure to low doses of toxic agents are difficult to recognize, because there are few, if any, early warning signs and, when signs are ultimately observed, they often imply irreversible effects. For example, cancer induction in experimental animals, even with the most potent carcinogenic chemicals, requires at least several months and in many instances a whole lifetime. There are at present no easy, straightforward methods for extrapolating even chronic exposure experimental data to calculate risks to large human populations. Teratogenic effects are easier to establish by animal experimentation, but there are similar uncertainties in extrapolating to human populations. Mutagenic effects are difficult to assess experimentally in mammals, and such effects are particularly insidious, in that they appear only in later generations.

Various measures used in assessing acute toxicity—such as LD_{10}, LD_{50}, and maximal tolerated dose—are generally found to be quantitatively similar in most animals. On the basis of dose per unit of body surface, toxic effects in man are in the same range as those in experimental animals, such as mouse, rat, hamster, dog, and monkey. On a body-weight basis, man is generally more vulnerable than the experimental animal, probably by a factor of 6–12. Comparative studies have shown generally that the absorption, metabolism, and excretion of various drugs are slower, dose for dose, in man; that there is greater retention of such drugs; and that higher concentrations occur in body fluids and tissues in man than in small mammals. With an awareness of these quantitative differences, appropriate safety factors can be applied to calculate relatively safe therapeutic dosages for man. These methods and principles of classical toxicology are useful for assessing toxic effects that are reversible and that are not progressive. They are much less useful in dealing with all of the problems of chronic irreversible toxicity or the effects of long-term exposure. This subject has not been considered widely in the past.

From the review of available information, two major questions emerge: "What types of experimental assay procedures are required for a valid assessment of chronic toxicity of chemicals in experimental animals?" "How can such data be extrapolated to estimate risks in humans?" In dealing with these questions, our recommendations are restricted to a specific risk—namely, cancer—with the understanding that the same considerations will apply, at least partially, to the problems of mutagenesis and teratogenesis. Furthermore, we consider only carcinogens whose mechanisms involve somatic mutations.

Some principles that underlie efforts to assess the irreversible effects of long-continued exposure to carcinogenic substances at low dose rates are outlined below.

PRINCIPLE 1

Effects in animals, properly qualified, are applicable to man. This premise underlies all of experimental biology and medicine: But, because it is continually questioned with regard to human cancer, it is desirable to point out that cancer in men and animals is strikingly similar. Virtually every form of human cancer has an experimental counterpart; and every form of multicellular organism is subject to cancer, including insects, fish, and plants. Although there are differences in susceptibility between different animal species, between different strains of the same species, and between individuals of the same strain, carcinogenic chemicals will affect most test species; also large bodies of experimental data indicate that many chemicals that are carcinogenic to animals are likely to be carcinogenic to man, and vice versa.

Evidence that circumstances leading to cancer induction in humans are also applicable to experimental animals stems from the very first observation of chemical carcinogenesis—the appearance of cancer of the scrotum in chimney sweeps, observed by the British surgeon, Percival Pott, in 1775. It was not until modern times that a substance implicated in human cancer was found to be carcinogenic in animals: When Japanese scientists found in 1915 that extracts from coal tar cause cancer when applied to the skin of experimental animals. Many pure carcinogenic chemicals have since been isolated from a wide variety of "tars" derived from incomplete combustion of organic matter, such as coal, wood, and tobacco. There is little doubt that these and other chemicals, alone or in combination, are responsible for the greatly increased incidence of lung cancer among smokers. With the possible exception of arsenic and benzene, all known carcinogens in man are also carcinogenic in some species, although not in all that have been tested. However, all carcinogens in animals are not known to cause cancer in humans.

PRINCIPLE 2

Methods do not now exist to establish a threshold for long-term effects of toxic agents. With respect to carcinogenesis, it seems plausible at first thought, and it has often been argued, that a threshold must exist, below which even the most toxic substance would be harmless. Unfortunately, a threshold cannot be established experimentally that can be applied to a total population. A time-honored practice of classical toxicology is to establish maximal tolerated (no-effect) doses in humans on the basis of finding a no-observed-adverse-effect dose in chronic experiments in animals and to divide this dose by a "safety factor" of, say, 100, to designate a "safe" dose in humans. There is no scientific basis for such estimations of safe doses in connection with carcinogenic effects. For example, even if *no* tumors are obtained in an assay of 100 animals, this means only that at a 95 percent confidence level the true incidence of cancer in this group of animals is less than 3 percent. Even if we were to use 1,000 animals for assay, and no tumors appeared, we could only be 95 percent sure that the true incidence was less than 0.3 percent. Obviously, 0.3 percent is a very high risk for a large human population.

In fact, there are no valid reasons to assume that false-negative results of carcinogenicity tests are much less frequent than false-positive ones. To dismiss all compounds that did not induce tumors in one or two mouse and rat experiments as noncarcinogenic is wrong. Labeling as "carcinogens" all substances that gave rise to increased incidence of tumors is justified only if there is also evidence of a causal relationship. The "relative risk" of compounds that are not found to induce tumors in animal experiments must also be considered. But this requires evaluation of data other than those collected in chronic toxicity studies on rodents.

Experimental bioassays in which even relatively large numbers of animals are used are likely to detect only strong carcinogens. Even when negative results are obtained in such bioassays, it is not certain that the agent tested is unequivocally safe for man. Therefore, we must accept and use possibly fallible measures of estimating hazard to man. This reasoning leads us to the statement of Principles 3 and 4.

PRINCIPLE 3

The exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in man. The most commonly expressed objection to regulatory decisions based on carcinogenesis observed in animal experiments is that the high dosages to which animals are exposed have no relevance in assessment of human risks. It is therefore important to clarify this crucial issue.

Practical considerations in the design of experimental model systems require that the number of animals used in experiments on long-term exposure to toxic materials will always be small compared with the size of the human populations similarly at risk. To obtain statistically valid results from such small groups of animals requires the use of relatively large doses so that the effect will occur frequently enough to be detected. For

example, an incidence as low as 0.01 percent would represent 20,000 people in a population of 200 million and would be considered unacceptably high, even if benefits were sizable. To detect such a low incidence in experimental animals directly would require hundreds of thousands of animals. For this reason, we have no choice but to give large doses to relatively small experimental groups and then to use biologically reasonable models in extrapolating the results to estimate risk at low doses. Several methods for making such calculations have been considered and used, but we think that the best method available to us today is to assume that there is no threshold and that a direct proportionality exists between the size of the dose and the incidence of tumors. However, it is important to recognize that such a calculation may give either too small or too large an estimate of risk. The actual risk to humans might be even greater over a human lifetime, because it is about 35 times that of a mouse; and there is evidence that the risk of cancer increases rapidly with the length of exposure. Moreover, experimental assays are conducted under controlled dietary and environmental conditions with genetically homogeneous animals, whereas humans live under diverse conditions, are genetically heterogeneous, and are likely to include subpopulations of unusual susceptibility.

It should be emphasized that these general considerations give only a minimal estimate of human risk; moreover, they do not take into consideration differences in susceptibility between species. For example, beta-naphthylamine is well established as a human carcinogen on the basis of epidemiological studies of occupationally exposed workers, whereas experiments have not shown it to be carcinogenic, for example, in the hamster, which is relatively resistant.

Not all substances that cause a given incidence of cancer in experimental animals are equally carcinogenic for man. This means that results of studies of chronic toxicity, which are imperfect assay systems for carcinogenicity testing, should not be used as the sole criteria in the assessment of risk.

PRINCIPLE 4

Material should be assessed in terms of human risk, rather than as "safe" or "unsafe." The limitations of the current experimental techniques do not allow us to establish safe doses, but with the help of statistical methods we may be able to estimate an upper limit of the risk to human populations. To calculate such a risk, we need data to estimate population exposure: a valid, accurate, precise, and reproducible assay procedure in animals; and appropriate statistical methods. Several general guidelines may be presented. First, no rigid, generally applicable procedure can be recommended for testing all toxic agents. Substances differ too much in their overall effects, and it will ultimately have to be left to the well-informed judgment of expert investigators to design appropriate assays. If substances that affect large populations are found to be carcinogenic, experiments of much wider scope may have to be conducted, to obtain more detailed information on their possible effects in humans. As a pragmatic guideline, it would be desirable to test a compound for carcinogenicity in at least two species, such as the mouse and the rat, and the strains of animals used should have a rather low incidence of spontaneous tumors under the conditions of the test. It is important to include "positive" controls, with known carcinogens, under the same conditions used for the test animals. This has been a point of considerable controversy.

Experiments should be conducted over as much as possible of the lifetime of the experimental animal. The highest dose should be the maximum that is tolerated without shortening the lifespan through causes other than cancer. Every animal, whether it dies during the exposure period or is sacrificed at the end of the experiment, should be examined grossly and microscopically, and all toxic effects (not only cancer) should be noted.

Risk constitutes but half the essential comparison that should be made in the assessments of human hazard; the other half is benefit to the exposed population of the agent whose hazard has been identified. Decisions cannot involve merely the risk. But the acceptability of risk should depend on the specific benefits derived, the nature of the population exposed, and the availability of practical alternatives.

It is not possible to guarantee a risk-free society; nor is a risk-free society necessarily the most desirable society. It is often necessary to accept the risks of chemicals—such as drugs and pesticides—when the benefits warrant their use. Risks imposed on persons who gain no benefits are generally not acceptable. Personal choice and personal values enter into the risk-benefit comparison. For major benefits—for example, in the treatment of otherwise incurable or incapacitating diseases—much higher risks are allowable than otherwise. An important principle in risk-benefit assessment is that each person must be allowed the widest possible choice, supported by full information on risks, as well as benefits, so that intelligent choices may be made.

The benefit portion of the equation should be well defined by knowledgeable experts and based on data at least as good as the risk data. It is important, therefore, that the benefit-risk comparisons be established with the active cooperation of those who are qualified to assess the usefulness of a substance and the consequences to those in need of it, as well as to the population at large.

Finally, mankind is already exposed to many carcinogens whose presence in the environment cannot easily be controlled. In view of the nature of cancer, the long latent period of its development, and the irreversibility of chemical carcinogenesis, it would be highly improper to expose the general population to an increased risk if the benefits were small or questionable, or were restricted to limited segments of the population.

ESTIMATION OF RISK

Chronic low-dose-rate toxicity was assessed quantitatively by different procedures, the method chosen depending on the character of the experimental evidence and whether the substance in question was judged to be carcinogenic or not.

Assessments of the toxicity of noncarcinogenic substances are described in the sections on Inorganic Solutes and Organic Solutes. These are expressed as estimates of maximal "no-observed-adverse-effect" concentrations in water, and are based on the assumption that, for these noncarcinogenic materials, there are threshold doses below which no adverse effects on health are likely to occur.

Risks of exposure to radionuclides and carcinogenic organic compounds were estimated by methods that involve an assumption that there are no thresholds in the dose-response relationships. In the case of radionuclides, the estimates were based, in large measure, on the report of the Advisory Committee on the Biological Effects of Ionizing Radiation (National Academy of Sciences-National Research Council, 1972); the method used for organic compounds is described below.

In the case of organic compounds that were identified as carcinogens, the risk to man was expressed as the probability that cancer would be produced by continued daily ingestion, over a 70 y lifetime, of 1 liter of water containing a standard quantity (1 μg/liter) of the substance in question. Estimates expressed in this form may then be used to calculate risk due to the concentrations actually found in drinking water.

To make such estimates from the results of animal feeding studies two steps are necessary. The first involves conversion of the standard human dose to the physiologically equivalent dose in the animal, and this was performed on the basis of relative surface area. The second step requires use of a risk model relating dose to effect. The model used for this purpose is

$$P(d)=1-e-(\lambda_0+\lambda_1 d+\lambda_2 d^2+\cdots\lambda_k d^k)$$

where P(d) is the lifetime probability that dose d (total daily intake) will produce cancer,

K = the number of events in the carcinogenic process

and λ_0, λ_1, λ_2—etc., are nonnegative parameters. At low doses, the higher order terms in d^2, d^3, etc. may be neglected and

$$P(d)\simeq 1-e-(\lambda_0+\lambda_1 d)\simeq\lambda_0+\lambda_1 d$$

λ_0 representing the background rate. When two or more sets of results of lifetime animal feeding studies were available, experimental values of P(d), the fraction of test animals developing cancer, and d, the total daily dose, were fitted to the equation to determine how many of the terms λ_0, $\lambda_1 d$, $\lambda_2 d^2$, etc. were necessary to give the best fit. Corresponding values of λ_0, λ_1, or λ_0, λ_1 and λ_2, etc. were used to calculate P(d) for the low dose of interest, namely the animal dose that was physiologically equivalent to the standard dose for man. If the animal experiments involved only one dose level, the $\lambda_1 d$ term, alone, was used in the calculation. Upper confidence limits on the estimated low-dose risk were also calculated by use of maximum-likelihood theory, and these values were tabulated.

Since the animal data were obtained from lifetime feeding studies, the risk estimates calculated from them for the low doses that were estimated to be physiologically equivalent to the human dose, were taken to represent the lifetime risks for man. The background rate, obtained from the cancer incidence in the control groups of experimental animals and represented by the parameter λ_0, was excluded from the tabulated values of P(d), which therefore represent the incremental risks due to ingestion of the compounds in water.

RECOMMENDATIONS FOR RESEARCH

A research program should include the following:

1. Studies of the physiological and biochemical mechanisms by which the toxic substances in water produce their effects.

2. Development of rapid, inexpensive, and precise tests to identify substances that may produce important toxic effects at low doses and dose rates.

3. Epidemiological studies of chronic disease.

4. Research on statistical methods and analytical models for describing and estimating the effects of long exposure to low doses of toxic substances. Studies should not be limited to carcinogenesis and should consider, also, differences between species, and particularly sensitive subgroups in the population.

MICROBIOLOGY OF DRINKING WATER

Outbreaks of waterborne disease are reported to the National Center for Disease Control (CDC) of the United States Public

Health Service by state health departments. In addition, EPA obtains information about outbreaks from state water supply agencies. Data on waterborne outbreaks have limitations and must be interpreted with caution. They represent only a small part of a larger public health problem. The number and kind of reported outbreaks may depend upon the interest or capabilities of a particular state health department or individual. They do not provide the true number of outbreaks, cases or causes of disease associated with drinking water.

No law or regulation requires state authorities to report all cases of gastroenteritis to CDC, and, in fact, many small outbreaks are not reported to state departments of health. Moreover, etiologic agents are seldom identified, even in the cases that are reported. There are reasons to believe that most outbreaks of waterborne disease are of microbiological origin. Yet the accuracy of epidemiological studies is limited by underreporting and diagnostic uncertainties.

The microbiological contaminants selected for consideration are those for which there is epidemiological or clinical evidence of transmission by drinking water. These include a variety of bacteria, viruses, and protozoa. Methods of detecting these contaminants in drinking water are reviewed, together with the determination of permissible levels. Because current drinking water standards place major emphasis on detection of microbiological contaminants, considerable attention is devoted to the validity and health significance of microbiological standards.

Effective water treatment systems in the United States have had a major impact on the reduction of waterborne infectious diseases during this century. However, waterborne disease outbreaks continue to occur. In 1975, 24 outbreaks involving 10,879 cases were reported to the CDC, but no deaths. Acute gastrointestinal illness accounted for about 90 percent of the cases.

In 1971–1974, deficiencies in treatment, such as inadequate or interrupted chlorination, and contamination of ground water, were responsible for a majority (65 percent) of the waterborne disease outbreaks. In 1975 treatment deficiencies were responsible for most outbreaks. However, deficiencies in the distribution systems were responsible for most cases.

Control of waterborne epidemics depends largely upon the control of infectious enteric diseases. Much of the success in this regard can be attributed directly to the use of chlorine as a disinfectant. The use of chlorine in water treatment may result in the formation of compounds that are known carcinogens for animals and suspected carcinogens for humans, but the benefits gained are very great.

Several substitutes for chlorine have been suggested (e.g., ozone, chlorine dioxide, bromine and iodine) but much more research is required before any of them can be recommended as a sole substitute for chlorine in water treatment. Questions concerning disinfection effectiveness, toxicity of by-products, and residual in the distribution system must be answered for proposed substitutes as well as for chlorine. It may be possible to reduce the concentrations of undesirable organic by-products of chlorination, without compromising disinfection, by changing the sequence or rate of chlorine addition in relation to other steps in water treatment. Use of other oxidizing agents before chlorination may also help to modify organic matter before significant amounts of chlorinated derivatives can be formed.

BACTERIA

Bacteriological testing and observance of bacteriological standards are adjuncts to, not substitutes for, good-quality raw water, proper water treatment, and integrity of the distribution system. Application of the present coliform standards appears adequate to protect public health when raw water is obtained from a protected source, is appropriately treated, and is distributed in a contamination-free system.

Current coliform standards are not satisfactory for water reclaimed directly from wastewater. Meeting current coliform standards for water reclaimed directly from waste water, or for water containing several percent of fresh sewage effluent, is insufficient to protect public health. For such raw water supplies, new microbiological standards should be developed and applied as supplementary to coliform standards.

The standard plate count is not a substitute for total coliform measurements of the sanitary quality of potable water. It is, however, a valuable procedure for assessing the bacterial quality of drinking water. Ideally, standard plate counts (SPC) should be performed on samples taken throughout the systems. The SPC has major health significance for surface-water systems that do not use sedimentation-fluocculation-filtration and chlorination, and for those ground-water systems and do not include chlorination.

A research program is needed to increase the value of the relatively simple bacteriological tests in controlling the sanitary quality of drinking water. The program should include:

1. Epidemiological studies of water quality and health, with application of more sensitive methods for detecting pathogens in drinking water and better reporting of outbreaks of waterborne disease.

2. Development of membrane-filtration methods to allow testing of larger samples and to reduce interference by overgrowth and disinfectants.

3. Improvement of procedures for making total-plate-counts and study of the utility of such tests for assessing the health hazards of drinking water.

4. Research on more rapid and sensitive methods for detecting pathogens and the use of such methods for monitoring the quality of water.

VIRUSES

The bacteriological monitoring methods currently prescribed (coliform count, standard plate count) ar the best biological indicators now available for routine use in determining the probable levels of virus in drinking water. The strictest current standards of water treatment, diligently applied, can provide a high degree of assurance that viruses injurious to human health are not likely to be present in finished drinking water.

Because knowledge of the scale of potential viral contamination is scanty, and because there is no rigorous basis for establishing a harmless level of viral concentration in water, research on the problems of viral contamination should be strongly supported. In particular, the following subjects deserve special attention:

1. Methods for testing drinking water for viral contamination.

2. Methods for recovery, isolation, and enumeration of viruses (especially hepatitis A).

3. Specific etiology of viral gastroenteritis.

4. Methods for evaluating and improving effectiveness of present water treatment to remove or inactivate viruses.

5. Determination of the amounts of enteric viruses that must be ingested to produce infection and disease.

PARASITES

The most important waterborne parasitic diseases in the United States are amoebiasis and giardiasis. Known outbreaks of these diseases have resulted from sewage contamination in distribution systems, and from inadequately treated surface waters.

The cysts of both of these parasites are more resistant to chlorine than are bacteria, but flocculation and filtration can remove them. Nevertheless, knowledge of the vulnerability of these organisms to disinfection is incomplete, and, in particular, the conditions necessary for destruction of giardia cysts require further study. The same considerations apply to a few other parasitic protozoa that, although rare, have been identified in public water systems.

Metazoan parasites (helminths, nematodes) that can be present in raw water will be controlled in public water supplies by well-regulated flocculation, filtration, and disinfection.

TESTING

A deficiency of customary biological methods for evaluating the bacteriological quality of water is that results from tests are not known until after the water sampled has already entered the distribution system, and been used. Sudden invasions of contamination are unlikely to be detected promptly enough to prevent exposure, and may overwhelm the corrective treatments. Therefore, control of microbiological quality can be more readily achieved if the raw water supply is of high and relatively invariant quality.

Nevertheless, it is essential that present methods of microbiological testing be continued to validate the effectiveness of disinfection and for detecting defects within the system.

SOLID PARTICLES IN SUSPENSION

Materials suspended in drinking water include inorganic and organic solids as finely divided particles of sizes ranging from colloidal dimensions to more than 100 micrometers. Such particles may also have other substances and micro-organisms attached to them.

Small particles of some materials, such as the asbestos minerals, may have the potential to affect human health directly when they are ingested, and there is widespread concern over the biological effects of such substances.

Many kinds of particles, though apparently harmless in themselves, may indirectly affect the quality of water by acting as vehicles for concentration, transport, and release of other pollutants.

Water treatment can often be effective in removing most of the suspended particles but conventional methods of detecting the presence of particulate material by measurement of turbidity have serious deficiencies.

DIRECT EFFECTS ON HEALTH

Particles of asbestos and other fibrous minerals occur in raw water, usually in a range of sizes from fractions of a micrometer to a few micrometers. Generally there are fewer than 10 million fibers per liter, but waters are found with from less than 10,000 to more than 100 million fibers per liter. Some of the highest counts have been found near some cities. Fibers in drinking water are typically less than 1 micrometer long and fibers longer than 2 micrometers are uncommon. Identification and counting of fibers is difficult and time-consuming, usually requiring the transmission electron microscope. The reported counts are highly variable, often differing from one count to the next by a factor of 10 or more.

Epidemiological studies of workers exposed to asbestos by inhalation have shown an increase in death rates from gastrointestinal cancer. With respiratory exposure it is likely that more fibers are swallowed than remain in the lungs. The workers studied were exposed to asbestos with a large range of fiber lengths. It is not clear whether fiber length

is pertinent to the development of cancer in the digestive tract in humans.

Epidemiological studies of cancer death rates in Duluth, Minnesota, where the water supply has been contaminated with mineral fiber, have so far not revealed any increase of gastrointestinal cancer with time, in comparison with death rates in other areas. Contamination of the Duluth drinking water began less than twenty years ago however, and since many cancers have long latency periods, these negative epidemiological findings do not exclude the possibility that an increase may appear within the next five to fifteen years.

Animal deposition model studies have shown that fiber length and diameter affect the carcinogenic response seen, the long thin fibers appearing to be the active ones. However, the relevance of these experimental models to the human experience is not clear. While some animal studies have shown penetration of the gastrointestinal epithelium, others have not.

It is not known whether other inorganic particulates that occur in water produce any direct effects on human health.

INDIRECT EFFECTS ON HEALTH

The concentration of inorganic, organic, and biological pollutants is usually much higher in the suspended solids and sediments of streams and lakes than in water. Clay, organic, and chiefly responsible for such concentrations. Clay and organic particulates have large surface areas and strongly adsorb ions, polar and nonpolar molecules, and biological agents. Occurrence of these materials in water is a consequence of natural events, as well as human activity, and is common in many waters that people drink. Although many of the clay or natural organic particulates, in themselves, may not have deleterious effects when ingested by humans, they may exert important health effects through adsorption, transport, and release of inorganic and organic toxicants, bacteria, and viruses. The clay or organic complex with a pollutant may be mobilized by erosion from the land, or complexes may form when eroded particulate matter enters a stream containing pollutants. The atmosphere is also an important pathway. In the adsorbed state, organic and inorganic toxicants may be less active; however, the possibility exists that the toxicants may be released from the particulate matter in the alimentary tract and then exert toxic effects. It is not clear how complexes of particulate matter with viruses and bacteria behave in the gut. It is known, however, that some enzymes retain their activity when adsorbed on clay, and that viral-clay particulates are infectious in tissue culture and in animal hosts.

TURBIDITY AS AN INDICATOR

A high turbidity measurement is an indication that a water may produce an adverse health effect; however, a low turbidity measurement does not guarantee that a water is potable. Turbidity measurements do not indicate the type, number, or mass of particles in a water supply. Where particulates in water are suspected of being harmful, the particulate content should be identified and counted by more specific techniques. Such techniques may include biological, organic, inorganic, and fibrous-particulate surveys.

Turbidity measurements are valuable for process control in water-treatment plants. However, the results obtained with present instruments, procedures, and units of measurement are not well correlated with particle concentrations and size distributions. The test itself must be standardized and refined to facilitate its use for this and other purposes.

CONCLUSION AND RECOMMENDATIONS

Certain mineral fibers found in water are suspected of being harmful upon ingestion. The available data with respect to asbestos orally ingested through drinking water do not suggest an immediate hazard to public health. They do suggest that additional research, both experimental (using animals) and epidemiological, is required to determine the degree of hazard. Until new results become available, contamination of drinking water by mineral fibers should be kept to a minimum through the use of effective coagulation and filtration processes and other appropriate measures.

Because particulates are vehicles for concentration, transport, and release of pollutants, they may have indirect effects on health. Coagulation and filtration are effective methods of reducing particulate concentrations. Measurement of particulate content by turbidimetry is imprecise and cannot be relied upon as a sole indicator of the safety of an uncharacterized drinking-water source.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. A survey of suspended particulate matter in raw and treated drinking-water supplies in several "typical" communities is urgently needed as background information. This must be coupled with analysis of accompanying organic and inorganic material and microorganisms, as well as characterization of the particulates with respect to size, shape, composition, and adsorbed constituents.

2. Ingestion studies should be carried out with fibers of various types and sizes distributions in validated animal model systems.

3. Epidemiological studies of time trends in death rates should be conducted in areas that have high concentrations of mineral fibers in drinking water.

4. Electron microscopy procedures for detecting and counting asbestos fibers should be scrutinized with respect to their specificity, precision and accuracy.

5. Information is required on the effects of inorganic, organic and biological toxicants adsorbed on clay and organic particulates.

6. Development of improved and standardized methods for determining particle concentrations and size distributions by optical techniques, such as light scattering and absorption, should be supported.

INORGANIC SOLUTES

The Interim Primary Drinking Water Regulations list maximum allowable concentrations for six metallic elements—barium, cadmium, chromium, lead, mercury, and silver. Ten additional metals were reviewed in this study—beryllium, cobalt, copper, magnesium, manganese, molybdenum, nickel, tin, vanadium, and zinc. Sodium, which is also a metal, was considered separately, because the problems its poses are quite distinct from those associated with the other metallic substances.

Eight of these metals are known to be essential to human nutrition: chromium, cobalt, copper, magnesium, manganese, molybdenum, tin and zinc. Nickel and vanadium probably are essential also, and it is possible that barium can be beneficial under certain conditions. The metals, beryllium, cadmium, lead, mercury and silver are believed not to be essential to humans.

Elements that are beneficial in small quantities often exhibit toxic properties when ingested in excessive amounts or concentrations. In assessment of the adverse health effects of such materials it is important not to overlook deficiency problems that might be encountered if the substances were to be completely eliminated from water supplies.

Trace metals, usually in the form of ions, occur in water both as a result of natural processes and as a consequence of man's activities. Ground waters, because of long contact with rocks and mineralized soils, usually contain greater concentrations of trace metals than surface waters. There is considerable temporal and spatial variation in concentrations of trace metals in surface waters. Generally, the trace metal concentrations of rivers tend to increase from source to mouth, and to vary inversely with discharge.

Of the 16 metals studied, the relative contribution of man's activities to the concentrations found in water supplies can be rated roughly as follows: Very great—cadmium, chromium, copper, mercury, lead and zinc; high—silver, barium, molybdenum, tin; molerate—beryllium, cobalt, maganese, nickel and vanadium; low—magnesium.

Other important sources of trace metals in drinking water are chemicals used in water-treatment processes and pickup of metallic ions during storage and distribution. Although a large fraction of the United States population continues to receive water from ground sources or from impounded upland sources without treatment other than disinfection, most large surface supplies are subjected to treatment that includes coagulation, sedimentation, filtration, and disinfection. Should trace metals occur in the raw water supply, these normal water-treatment processes have either no effect or an uncertain one on the usual low-level concentrations of these metals. Moreover, probable trace metal impurities in the technical-grade chemicals used to treat water may introduce additional amounts.

A wide variety of materials including several metals, alloys, cements, plastics, and organic compounds are used in the pumps, pipes fittings, and reservoirs of distribution and plumbing systems. Reactions, particularly of soft, low-pH waters, with materials of distribution system often have produced much greater concentrations of iron, copper, zinc, lead and cadium at the tap than those at the treatment plant.

Adverse health effects associated with trace metals depend upon the total intake from all sources—food, air and water. As a general rule concentrations of trace metals in foodstuffs greatly exceed those found in drinking waters. Because the diet of most of the United States population is increasingly varied and comes from diverse geographical sources as a result of modern food-distribution practices that counterbalance local excesses or deficiencies, the dietary intake of trace metals exhibits relatively small variation throughout the United States. This factor is helpful in evaluation of maximum no-observed-adverse-health-effect concentrations for drinking water.

Airborne exposure to trace metals other than lead is largely occupational, occurring through the inhalation of industrial dusts or fumes. At present there is more general exposure to lead from motor-exhaust fumes although evidence for acute and chronic health effects is derived from occupational exposures. Because the data relate primarily to healthy adults, caution must be observed in extrapolating these data to the general public.

All the trace metals studied are known to exhibit toxic effects at some level of intake. Many of these effects are observed, however, only at concentrations greater than the maxima that have been found in drinking water. To include such materials in primary drinking-water standards, with the accompanying requirement for mandatory surveillance, does not confer any health benefit. Augmenta-

tion of the natural concentrations of these trace elements to values of concern can be avoided most readily by preventing discharge of the contaminants into water sources.

In addition to the trace metals mentioned above, the effects on health of several other inorganic constituents of drinking water were also studied. These include sodium, arsenic, selenium, fluoride, nitrate and sulfate. The relationship between water hardness and health was also considered. The findings on these topics are summarized individually below.

Barium. It is rare to find barium in drinking water at a concentration in excess of 1 mg/liter because of the low solubility of barium sulfate. Natural and treated waters usually contain sufficient sulfate so that more than 1–1.5 mg/liter of barium cannot be maintained in solution.

Acid-soluble barium salts are very toxic, whereas insoluble compounds are benign. There has been no determination of the chronic effects of low levels of barium ingested over a long period of time.

The Interim Primary Standard of 1 mg/liter for barium has been based on extrapolation from effects of industrial exposure to dusts of soluble barium salts. Insufficient data are available to estimate maximum no-observed-adverse-health effect concentrations on the basis of water intake. The limit of 4 mg/liter of the U.S.S.R. is based on organoleptic factors. International and European Standards of the World Health Organization (WHO) do not list barium.

It is recommended that animal studies involving long-term low-level ingestion of barium salts in water be carried out to determine possible health effects.

Beryllium. Because the oxide and hydroxide are relatively insoluble at the usual range of pH, beryllium is unlikely to occur in drinking water at more than trace concentrations. The sulfate and chloride are very soluble, but they hydrolyze quickly to the insoluble hydroxide.

Beryllium produces acute or chronic toxicity in animals when ingested continuously as beryllium sulfate in food in amounts greater than 10–20 mg/kg/day, or in water at concentrations greater than 5 mg/liter. Soluble beryllium has been shown to be transported in the bloodstream to bone, and to be able to induce bone cancer in animals, but the data are insufficient to allow estimation of risk.

Prolonged inhalation of dusts containing beryllium is known to produce pulmonary sarcoidosis. However, increased incidence of lung cancer has not been found among workers exposed to dusts containing beryllium.

No maximal allowable concentration for beryllium has been listed in the Interim Primary Drinking Water Regulations, nor has the WHO recommended a maximum limit. The U.S.S.R., however, has set a limit of 0.2 μg/liter. Until now the maximum concentration of beryllium found in U.S. surface waters has been 1.2 μg/liter and in finished U.S. drinking waters has been 0.17 μg/liter. Only 1.7 percent of drinking water supplies examined have been found to contain beryllium.

Additional studies of the frequency of occurrence and concentrations of beryllium in natural waters are needed to determine the extent to which it presents a hazard to health.

Cadmium. Cadmium is not known to be an essential or beneficial element. It has been found in 2–3 percent of U.S. surface waters, generally in concentrations not exceeding a few micrograms per liter because solubilities of cadmium carbonate and hydroxide are low at pH greater than 6. Only 0.1 percent of the supplies in the Community Water Supply Survey showed cadmium in excess of 10 μg/liter. In addition to its geological sources, cadmium enters water from the discharge of plating wastes and by corrosion of plumbing.

Food is the primary source of cadmium intake. Total daily intake from air, water, food and tobacco ranges from 40 μg/day for the rural nonsmoker on a low cadmium diet to 190 μg/day for the urban smoker on a high cadmium diet. Drinking water contributes only a small fraction (<5 percent) to this total intake.

Chronic ingestion of cadmium at levels greater than 100 μg/day, in combination with several other necessary predisposing factors, was found to be responsible for the onset of "Itai-Itai" disease in Japan. Dietary intake of amounts in excess of a milligram per day is needed for appearance of acute toxicity. Major toxic effects are on the kidney; data indicate that the toxicity of cadmium is related to the zinc:cadmium ratio within the organs. Both zinc and calcium may protect against cadmium toxicity. Persons deficient in these elements, and especially lactose-intolerant persons, who are also likely to be calcium-deficient, may constitute a high-risk group relative to cadmium. Some animal studies have shown carcinogenic and teratogenic effects, but dose-response relationships are unknown. Cadmium has also been implicated as a factor in hypertension.

Insufficient data are available for establishment of a maximum no-observed-adverse-health-effect value. It may be noted, however, that consumption of two liters/day of water containing 10 μg/liter of cadmium would contribute only about 20 percent of the normal total daily adult intake. Both the WHO and the U.S.S.R. have set the maximum allowable limit for cadmium at 10 μg/liter.

Chromium. Microgram amounts of chromium, derived primarily from food, are essential for maintenance of normal glucose metabolism. But chromium (VI) is known to be toxic, principally on the basis of information from respiratory occupational exposures. Increase risk of lung cancer among those occupationally exposed to chromium (VI) has been established.

Although inhaled hexavalent chromium may cause cancer of the respiratory tract, a working group of the International Agency for Research on Cancer concluded "there is no evidence that nonoccupational exposure to chromium constitutes a cancer hazard."

Concentrations of chromium found in natural waters are limited by the low solubility of chromium (III) oxides. A study of more than 1,500 surface waters showed a maximum chromium content of 0.11 mg/liter, with a mean of 0.01 mg/liter.

Little information is available about the average total daily intake of chromium in the United States, although it appears to be in the range of 60–280 μg/day. It has been suggested that diets containing mostly processed foods may be chromium-deficient. Tissue chromium in U.S. adults has been shown to decline with age.

In addition to the beneficial effect of chromium on glucose metabolism, some animal studies indicate that chromium deficiency may induce atherosclerosis.

Toxicity of chromium depends on the valence. No toxic effects were observed in rats when drinking water contained 25 mg/liter of trivalent chromium for a year or 5 μg/liter for life. Acutely toxic doses of trivalent chromium fall in the range of grams per kilogram of body weight. Hexavalent chromium was also tolerated at the 25 mg/liter level for a year by rats. Dogs showed no effects with 11 mg/liter over a 4-year period. Higher doses are toxic, however, producing erosion of the gastronintestinal tract and kidney lesions.

The maximum limit of the Interim Primary Drinking Water Regulations, 0.05 mg/liter, is only one-hundredth of the maximum no-observed-adverse-health effect concentration. The European Standards of the WHO and Japanese Standards give the same limit as acceptable, but set it in terms of hexavalent chromium only. The U.S.S.R. has limits of 0.1 mg/liter chromium (VI) and 0.5 mg/liter total chromium, based on organoleptic factors.

More information is needed on the carcinogenic potential of ingested chromium (VI) and chromium (III). If it becomes clear that highly toxic or carcinogenic effects occur only with chromium (VI), and a suitably sensitive analytical technique is available, then the standard might be set for chromium (VI) alone. In view of the trend in the United States toward dietary chromium deficiency, and the suggestion that chromium protects against atherosclerosis, it seems advisable to determine whether concentrations greater than that prescribed by the current drinking-water regulations are without adverse health effects, as some animal experiments suggest.

Cobalt. Cobalt is an essential element as a component of vitamin B_{12}. Excessive intake of cobalt may be toxic, however, as shown by the association of congestive heart failure with the consumption of beer containing about 1.5 mg/liter of cobalt.

Cobalt has been observed in natural waters only in trace amounts. Most waters contain no detectable cobalt, and values greater than 10 μg/liter are rare. The maximum concentration recorded in several extensive studies was 99 μg/liter.

The major source of cobalt is food; concentration in green leafy vegetables may be as greater as 0.5 mg/kg dry weight. Normally, less than 1 percent of total intake of cobalt is derived from aqueous sources.

Acute toxic effects in animals have been observed only at daily doses greater than several mg/kg of body weight. Chronic cobalt toxicity has been observed in children taking cobalt preparations to correct anemia at daily doses of 1–6 mg/kg body weight.

The Interim Primary Drinking Water Regulations do not list cobalt, nor has the WHO recommended a limit in its International or European standards. The U.S.S.R. has set a limit of 1 percent mg/liter.

Because the maximum no-observed-adverse-health-effect concentration is more than an order of magnitude greater than that found in any natural water or drinking water supply, there appears to be no reason at present to regulate the concentration of cobalt in drinking water.

Copper. Copper is an essential element for both plants and animals; it is a component of several enzymes that perform important iological functions.

Copper is a minor constituent of natural waters. In a survey of 1,600 surface waters of the United States, the concentrations were 1–280 μg/liter. Corrosion of copper piping may increase concentrations in drinking waters to several mg/liter. Copper may also be released into water in industrial discharges, and has been used for algal control in reservoirs at a few tenths milligram/liter.

Average total intake of copper is about 2.5 mg/day, so that when water contains more than 1 mg/liter of copper, the intake from water may equal or exceed that from food.

The general health hazard from copper intake at a few milligrams/liter appears to be small, but a few people are adversely affected by ingestion of even trace amounts of copper. This disorder of copper metabolism, called Wilson's disease, can be arrested by the use of chelating agents. Individuals with deficiency of glucose-6-phosphate dehydrogenase may be sensitive to copper.

The USPHS Drinking Water Standards (1962) recommended a limit for copper of 1 mg/liter based on organoleptic rather than health effects. Because no general adverse

health effects have been observed at the organoleptic limit and because the few individuals with metabolic deficiency are at the mercy of total copper intake rather than copper in water, there is no hygienic reason to impose a limit lower than the presently accepted secondary standard.

Lead. No beneficial effects of lead on human or animal development have yet been found. Although acute lead poisoning is rare, chronic lead toxicity is severe and occurs even with low daily intake (<1 mg) because of its accumulation in bone and tissue.

The natural lead content of surface waters is generally small. In a survey of nearly 1,600 raw surface waters 20 percent were found to contain detectable concentrations of lead and these had a mean value of 0.023 mg/liter. The lead concentration in municipal supplies at the tap may be much greater, however, for soft, low-pH (aggressive) waters dissolve lead from service connections, lead-lined household piping or soldered joints. Lead concentrations in excess of the interim level of 0.05 mg/liter were found in 1.4 percent of the water systems examined in the Community Water Supply Survey. The maximum value was 0.64 mg/liter.

The mean concentration of lead in U.S. drinking waters has been estimated to be 0.013 mg/liter. Consumption of 2 liters/day per capita gives a mean daily intake of 26 μg.

Lead intake from food varies greatly; mean daily values are estimated to be 100–300 μg per capita for adults. Average intake in water is considerably less than that from food, but when the concentration in water is close to or exceeds the interim level of 0.05 mg/liter, intake in water approaches that from food.

Absorption of lead from dietary sources, either food or water, is estimated to be about 10 percent for adults. Daily lead absorption from food is, then, 10–30 μg, while absorption from water ranges from an average of 3–10 μg or more, when water containing 0.05 mg/liter or greater is ingested at 2 liters/day.

The daily intake from air also ranges widely, and is greatest among city dwellers. For a daily inspiration volume of 20 m^3 for adults and a lead concentration of 3 $\mu g/m^3$ in urban air, the per capita daily intake is 60 μg. Absorption from air is about 40 percent, however, so that the daily quantity absorbed is 24 μg, a value comparable with the dietary absorption.

The sum of the estimated absorptions from the various routes, 50–60 μg/day, is already at the maximum no-observed-adverse-health-effect value of 50–60 μg/day.

Children, and especially inner-city urban children, are a special risk group with regard to lead toxicity. A primary reason is that absorption of lead from food and water is 40–50 percent for 2–3 year old children, rather than the 5–10 percent characteristic of adults. Also, water intake per kilogram of body weight is considerably greater for young children than for adults. Moreover, lead concentrations in urban air increase with proximity to the ground, so that urban children tend to have increased intake from this source. Young children also have the added risk of ingestion of flaking lead-based paints especially in depressed, older, urban areas.

Dietary lead intake for a 2-year old child (12 kg) has been estimated to be 100 μg/day (8.3 μg/kg/day); with water at the present 0.05 mg/liter limit and a consumption of 1.4 liter/day, and with air intake about 18 μg/day, the estimated total intake for a 2-year old would be close to 190 μg/day, not including other possible sources.

Major chronic adverse effects of lead are produced in the hematopoietic system, central and peripheral nervous systems, and kidneys. Disturbance in heme synthesis is considered to be the most sensitive effect. There is a detectable increase in red-cell protoporphyrin in women and children with blood lead concentrations greater than about 25–30 μg/dl (micrograms per deciliter). For men occupationally exposed, the maximum no-observed-adverse-health effect level appears to be somewhat greater at 50–60 μg/dl.

Results of studies in the Boston area indicate that increased blood levels of lead occur in children when the water supply contains 0.05–0.1 mg/liter of lead. Thus, the interim limit of 0.05 mg/liter may not provide a margin to safeguard the high-risk population in urban areas. The WHO recommendation of 5 μg of lead per kg/day as a safe total daily intake cannot be met for a 12 kg child when the water supply contains as much as 0.05 mg/liter. It is concluded that the no-observed-adverse-health-effect level cannot be set with assurance at any value greater than 0.025 mg/liter.

Manganese. Manganese resembles iron in its chemical behavior and occurrence in natural waters, but is found less frequently and usually at lower concentrations than iron. Manganese, like iron, is an essential trace nutrient for plants and animals. It is not known whether human manganese deficiency occurs in the United States. The solubility of the several oxidation states of manganese (II, III, and IV) depends upon pH, dissolved oxygen, and the presence of complexing agents. Occasionally, deep lakes or impounding reservoirs that contain organic sediments under anerobic reducing conditions can distribute several mg/liter of Mn^{+2} throughout the water body during "turnover" mixing. Normally, however, the concentration of manganese in natural surface waters is less than 20 μg/liter.

Manganese can be absorbed by inhalation, ingestion, and through the skin; the consequences of this have been recently reviewed in depth by the National Academy of Sciences. It has been known that the occupational inhalation of manganese dusts results in a disease of the central nervous system resembling Parkinsonism, and a form of pneumonia.

Ingestion of manganese in moderate excess of the normal dietary level of 3–7 mg/day is not considered harmful. A reported outbreak of manganism in Japan was attributed to drinking well water containing about 14 mg/liter of manganese.

The maximum concentration of manganese found in the 1975 Survey of Interstate Water Supply Systems was 0.4 mg/liter except for samples from two Alaskan airports which showed 1 and 1.1 mg/liter. A total of 669 supplies were examined. Similarly, the maximum concentration found in the 1969 Community Water Supply Survey was 1.3 mg/liter from 969 supplies. Both these maximum concentrations are an order of magnitude less than minimum concentrations at which adverse health effects are observed. Moreover, even with manganese at 0.4 mg/liter the intake of manganese from water would be only about 15 percent of the normal total dietary intake of manganese.

Because concentrations of manganese found in water supplies are much less than those at which adverse health effects have been observed and because the regulation of manganese for esthetic and economic reasons is also far more stringent than would be required for reasons of health, there seems little need to establish a maximum no-observed-adverse-health-effect value.

Magnesium. Magnesium is an essential element in human, animal, and plant nutrition. It is geologically ubiquitous and its salts are widely used industrially. The average U.S. adult ingests between 240–480 mg/day of magnesium. Magnesium intake from 3.6–4.2 mg/kg of body weight is believed to be adequate to maintain magnesium balance, which is closely regulated by normal kidneys. The median concentration of magnesium in the water of the 100 largest U.S. cities was reported at 6.26 mg/liter with a maxium of 120 mg/liter. It can be greater, especially in arid western states.

An excess of magnesium in the diet is seldom harmful, for it is generally excreted promptly in feces. High concentrations of magnesium sulfate in drinking water have a cathartic effect on new users, but a tolerance is soon acquired. Excessive magnesium in body tissues and extracellular fluids occurs only as a result of severe kidney malfunction. Magnesium deficiency in humans may occur in alcoholics, persons performing hard labor in hot climates (because magnesium is excreted in perspiration), those with certain endrocrine disturbances, and patients using potent diuretics. Such deficiencies can best be overcome by oral administration of magnesium compounds.

The National Interim Primary Drinking Water Regulations contain no limit for magnesium, nor did the 1962 USPHS Drinking Water Standards. The U.S.S.R. has set no limit, but the WHO has recommended a maximum of 150 mg/liter. In view of the fact that concentrations of magnesium in drinking water less than those that impart astringent taste pose no health problem and are more likely to be beneficial, no limitation for reasons of health appears needed.

Mercury. Mercury is a comparatively rare element. Its inorganic compounds are relatively insoluble and can exist in solution only in extremely small concentrations under natural conditions. Recent measurements show that only 4 percent of water supplies contain mercury at concentrations greater than about 1 μg/liter and only one of these exceeded the current standard of 2 μg/liter. Concentrations in these supplies range from 0.1–10 μg/liter. Industrial use of mercury has resulted in increased environmental contamination. The health effects of populations occupationally exposed to mercury and mercury compounds have long been recognized, but contamination of the general environment is of recent origin.

Inorganic mercury in bottom sediments can be transformed biochemically to injurious methylmercury or other organic mercurial compounds. The organic form readily enters the food chain with concentration factors as great as 3000 in fish.

Several investigators have estimated the blood levels of mercury at which identifiable symptoms of mercury intoxication occur. These levels may be obtained with a steady mercury intake of from 4–14 μg/kg/day. This would be 240–840 μg/day for adults and 80–280 μg/day for children.

It is estimated that the normal diet contributes about 10 μg/day of mercury. With daily intake of 10 μg from food and 4 μg from water it appears that there is considerable margin of safety. However, those individuals regularly consuming fish from contaminated areas may exceed the normal intake by a factor of three or more and thus constitute a high-risk population.

There is no indication that concentrations of mercury in drinking water or air have contributed in any significant way to methylmercury intoxication of the general population. The interim level limits the daily intake to 3–4 μg/day. Nearly all public water supplies in the United States contain less than 1 μg/liter of mercury. The WHO has set no limit and the U.S.S.R. has a maximum permissible concentration of 5 μg/liter.

Molybdenum. Soluble molybdate ions are present in trace concentrations in many surface waters, primarily as a result of discharge of industrial wastes but also as a product of natural weathering of molybdenum-bearing soils. Both suspended insoluble molybdenum disulfide and soluble molybdates are present in streams draining areas where molybdenum ore is mined and and processed, especially in Colorado and New Mexico.

Typical diets contain on the order of 100–1,000 μg/kg, whereas typical surface waters (except those draining mining areas) contain less than 100 μg/liter, with median values about 10 μg/liter. Hence, in most locations, water is a minor factor in the total molybdenum intake. However, some finished waters are reported to contain as much as 1.0 mg/liter, and so may provide as much as 2,000 μg/day of molybdenum. More information is needed about adverse health effects of molybdenum at these levels to deal properly with such supplies.

Molybdenum poisoning has rarely been observed in humans. Although it has been implicated for gout in Armenia and for a bone-crippling disease in India, more information is needed to establish cause-and-effect relationships.

Molybdenosis in livestock is a significant toxicological problem in many areas of the world. Consumption of molybdenum-rich forage by cattle and sheep causes severe diarrhea (scouring), which sometimes results in death. It can be prevented or alleviated by the administration of copper.

The U.S.S.R. has established a limit for molybdenum of 0.5 mg/liter in open waters, but the WHO has not promulgated a limit.

Nickel. Nickel may occur in water from trace concentrations of a few micrograms/liter to a maximum of 100 μg/liter. At these levels the daily intake of nickel from water ranges from less than 10 μg/day to a maximum of 200 μg/day, as compared to a normal food intake of 300–600 μg/day. Available information indicates that nickel does not pose a toxicity problem because absorption from food or water is low. The principal reason for considering nickel stems from epidemiological evidence that occupational exposure to nickel compounds through the respiratory tract increases the risk of lung cancer and nasal-cavity cancer. There is difficulty in separating the effect of nickel from the effects of simultaneous inhalation of other carcinogens including arsenic, chromium and cobalt.

Because of the generally low concentration of nickel in drinking water and its reported low oral toxicity, there is no present need to set primary health effect limits for nickel in water. WHO and the U.S.S.R. have set no standards for nickel in drinking water.

Silver. Trace amounts of silver are found in some natural waters and in a few community water supplies. It has not been detected at levels exceeding the interim standard of 50 μg/liter. Colloidal silver consumed in large doses—several hundred mg/kg of body weight can cause anemia and possibly death. The main chronic effect in man is "argyria". Argyria is a cosmetic defect once caused through medical or occupational exposure to silver preparations. Dosages of from 1–5 g of silver are sufficient to produce this syndrome.

On the assumption of 50% absorption of silver, consumption of 2 liters/day of water containing 0.005 mg/liter of silver would result in an accumulation of 1 g of silver over 55 years.

Silver ion has not been detected in water supplies in concentrations greater than half the no-observed-adverse-health-effect level.

Tin. There is some indication that tin may be a beneficial micronutrient, although it has not been conclusively demonstrated that tin is an essential trace element in human nutrition. Inorganic tin is relatively nontoxic, but organotin compounds can be toxic at high concentrations. Indeed, they are used as fungicides, insecticides, and anthelmintics.

Tin has seldom been determined in natural or municipally treated water. The few available data generally show concentrations of the order of 1–2 μg/liter. In contrast, tin is present in most natural foods, and especially in canned products, to the extent that the normal human ingestion varies from 1.0–30 mg/day which is three or more orders of magnitude higher than the probable amount in a liter of tap water.

EPA has not set a limit for tin in its National Interim Primary Drinking Water Regulations. In view of the foregoing considerations, no regulation seems necessary.

Vanadium. Vanadium is a trace metal which has been introduced into the environment in large quantities. Fresh surface waters show concentrations in the 2–300 μg/liter range, but with low frequency of detection. The data are limited on concentrations in finished drinking waters, but vanadium concentrations up to 19 μg/liter have been reported.

Occupational exposure to pentoxides and trioxides of vanadium leads to ear, nose and throat irritation and generally impaired health. The consequences of exposure to vanadium in air, water and food have been reviewed recently. There is no evidence of chronic oral toxicity.

Vanadium is considered a beneficial nutrient at μg/liter levels, and has been suggested as protective against atherosclerosis.

Zinc. Concentrations of zinc in surface water are correlated with man's activities and with urban and industrial runoff. The solubility of zinc depends upon the pH of the water. Concentrations ranging from 2–1200 μg/liter were detected in 77% of 1577 surface water samples and 3–2000 μg/liter in 380 drinking waters.

Zinc is relatively nontoxic and is an essential trace element. Recommended minimum intake levels are 15 mg/day for adults and 10 mg/day for children over one year of age. A wide margin of safety exists between normal intake from the diet and doses likely to cause oral toxicity. Concentrations of 30 mg/liter or more impart a strong astringent taste and a milky appearance to water. Some acute adverse effects have been reported from consumption of water containing zinc at 40–50 mg/liter. There are no known chronic adverse effects of low-level zinc intake in diet, but human zinc deficiency has been identified.

The proposed EPA secondary maximum contaminant level is 5 mg/liter.

Sodium. Sodium ion is an ubiquitous constituent of natural waters. It is derived geologically from the leaching of surface and underground deposits of salts such as sodium chloride, from the decomposition of sodium aluminum silicates and similar minerals, from the incorporation of evaporated ocean spray particles into rainfall and from the intrusion of sea water into fresh water aquifers. Sodium chloride used as a deicing agent on roads enters water supplies in runoff from roads and storage depots. This added sodium chloride amounting to 9 million tons in 1970, is distributed throughout the snow belt of the northern U.S. and is most heavily concentrated in metropolitan areas.

A survey of 2,100 supplies, covering approximately 50% of the population of the U.S., was carried out in 1963–1966. The concentrations of sodium ion found ranged from 0.44 to 1,900 mg/liter. About 42% of the supplies had sodium ion concentrations in excess of 20 mg/liter and nearly 5% had concentrations greater than 250 mg/liter.

Few studies of habitual sodium ion intake by healthy adults in the U.S. have been reported. Such data as have been reported are based on measurement of sodium excretion in 12- or 24-hour urine collections. Wide variations occur among individuals and in the same individual from day to day. One study reported a mean 24-hour excretion of 4,100 mg. with a range from 1,600 to 9,600 mg. in 71 working adult males in New York. Another study reported a mean sodium excretion near 2,800 mg/24 hours in 171 black women ranging in age from 35 to 44 years. Infants have been estimated to excrete 69–92 mg/kg/day.

Sodium chloride is added to many foods during processing. Additional sodium chloride is often added during cooking, and again at the table. None of this is essential, for habitual intake of sodium bears no relationship to physiological need. Healthy individuals have been shown to maintain sodium balance on an intake of less than 2,000 mg/24 hours while sweating 9 liters/day. A variety of pre-industrial societies, in widely divergent habitats (for example, tropical jungle, desert, arctic) subsist for generations on sodium intake less than 1,000 mg/day and show no evidence of sodium deprivation. Requirements for sodium in growing infants and children are estimated at less than 200 mg/day.

It thus appears that habitual intake of sodium in adults in the United States often exceeds body need by tenfold or more. Evidence that this excessive intake may have harmful consequences is summarized in the detailed report.

Specification of a "no-observed-adverse-health-effect" level in water for a substance such as sodium, for which the effect is associated with total dietary intake and for which usual food intake is already greater than a desirable level, is impossible.

Since adult fluid intake averages 1.5–3 liters/day, sodium intake from drinking water represents less than 10 percent of the habitual total intake of 3000–4000 mg so long as the sodium content of the water does not exceed 200 mg/liter. Adverse health effects may be anticipated with sodium concentrations in water greater than 20 mg/liter only for that special risk group restricted to total sodium intake of 500 mg/day, because it is not feasible to reduce intake from food below 440 mg/day. For this group, whose diets must be medically supervised, knowledge of the sodium ion concentration of the drinking water permits prescription of bottled water low in sodium when necessary.

Reduction in hypertension for a small segment of the U.S. population who are on severely restricted diets requires a total intake of sodium less than 500 mg/day. These persons need water containing less than 20 mg/liter sodium ion.

A larger proportion of the population, about 3 percent, is on sodium-restricted diets that require sodium intake of less than 2000 mg/day. The fraction that can be allocated to water varies, depending on medical judgment in individual instances. Knowledge of the sodium ion content of the water supply and maintenance of it at the lowest practicable concentration is clearly helpful in arranging diets with suitable sodium intake.

In many diets allowance is made for water to contain 100 mg/liter of sodium.

It appears that at least 40 percent of the population would benefit if total sodium ion intake were maintained at less than 2,000 mg/day: *Provided*, That sodium ion concentration in the water supply were less than 100 mg/liter, the contribution of water to the desired total intake of sodium would be 10 percent or less at a daily consumption of two liters.

Arsenic. Arsenic is not known to be essential to humans, nor are there known beneficial effects from its ingestion in any form, even though a number of arsenic compounds, principally organic, have been used medicinally for treatment of a number of diseases. Minimization of intake is, therefore, desirable.

Trace concentrations of arsenic are rather widely distributed in natural waters of the United States. Surface water surveys have indicated that 20 to 25 percent contain arsenic in excess of the detection limit of 10 μg/liter, and that concentrations as great as 1,000 μg/liter occur. Concentrations as great as 1,400 μg/liter have been reported for ground waters. Enhanced values for arsenic content have been encountered in the vicinity of smelters, and in connection with dumping or spills of arsenical pesticides.

Other sources of human intake of arsenic include residues of arsenical insecticides on fruits and vegetables, naturally occurring arsenic in food products such as shellfish, residual dietary organic arsenicals in pork and poultry, and inhalation of dusts containing arsenic from occupational or environmental contamination. The median total intake of arsenic from all sources in the United States has been estimated to be 137–330 μg/day.

The toxicity of arsenic depends greatly on chemical form, route of exposure, and the rate and duration of exposure. Arsines and trivalent inorganic arsenic (arsenite), are the most toxic forms. The lethal oral dose of sodium arsenite lies in the range of 1–25 mg/kg; arsenic trioxide is one-third to one-tenth as toxic, and pentavalent arsenic and organic arsenicals are less than one-tenth as toxic.

Chronic or sub-acute toxicity of arsenic has been observed with ingestion of a few milligrams per day for two weeks or longer. Initial symptoms are skin erythrema, edema and pigmentation, gastrointestinal and neurological disturbances. Similar symptoms have been observed in several populations that use water containing 100–1,000 μg/liter of arsenic. Other conditions attributed to excessive human intake of arsenic include neuropathy, increased heart attacks, and vascular injury leading to gangrene and "Blackfoot." Industrial exposures, by inhalation or skin contact, sufficient to cause serious effects on health, have been reported in the United States and several other countries.

Human exposure to inorganic arsenic compounds has been linked to development of cancer of the skin, respiratory system, and gastrointestinal tract. However, animal studies have not shown arsenic compounds to be carcinogenic even when administered at the maximally tolerated dosages for long periods of time. This absence of positive results from controlled animal studies makes it impossible to estimate quantitatively a risk of cancer from intake of arsenic in any form or concentration.

Arsenic compounds are fetotoxic in animals at high doses, and teratogenic at lower doses. They have also been found to be mutagenic and are associated with chromosomal aberration in man.

There is speculation that interactions between arsenic and heavy metals or between arsenic and irritating substances, such as sulfur dioxide, may be important in determining overall effects on humans exposed to mixtures of these environmental contaminants. Arsenic has been found to protect against selenium poisoning in some circumstances, but under other conditions selenium and arsenic appear to be additive in toxicity.

The maximum no-observed-adverse-effect-level for arsenic in water is less than 100 μg/liter. The current mandatory U.S. drinking water limit of 50 μg/liter provides only a meager margin of safety. Intake from 2 liters/day of water containing 20 μg/liter is slightly greater than 10 percent of the median total intake of arsenic. The present WHO limit is 50 μg/liter, as it is in the U.S.S.R.

A research program should include:

1. Improvement of analytical techniques and methodology for better adaptability to water and foods. (Definition of chemical form is required.)

2. Epidemiological and analytical studies of the distribution of the various forms of arsenic in water at low concentrations, and relationship to disease patterns.

3. Development of a suitable animal model for long-term studies of arsenic toxicity at low levels.

4. Intensive studies on the metabolism of arsenic in mammalian systems.

5. Studies on the itneraction of arsenic with other trace elements in the environment, such as Se, Cu, Zn.

Selenium. Either a deficiency or an excess of selenium can result in adverse responses. Selenium is an essential nutrient, part of the enzyme glutathione peroxidase, and may have a role in other biologically active compounds. It is a detoxifying agent for heavy metals, especially cadmium, and in some circumstances acts antagonistically to arsenic. On the other hand chronic exposure to excess selenium results in dermatitis, central nervous system and gastrointestinal disturbances. Large doses cause acute toxicity or death.

Most natural waters contain only minute concentrations of selenium, less than 10 μg/liter, but in regions with seleniferous soils concentrations in water may reach several hundred micrograms per liter, particularly for well water. One surface water receiving irrigation drainage from seleniferous soils has been found to contain 2000 μg/liter.

Most selenium intake normally is from food. Concentrations in foodstuffs vary widely, depending on the type and the selenium content of the soil in which the crop was grown. Cereals, meats, and seafoods are likely to be major contributors, with average concentrations of a few tenths of a mg/kg. Minimum nutritional requirements for selenium have been estimated to be 1 mg/month.

Industrial exposure to selenium may occur in copper refining, in the mining and milling of lead, zinc, phosphate, or uranium, in the manufacture of glass, ceramics, electronic devices and pigments, and as a result of coal or oil combustion. Atmospheric pollution and general respiratory intake may also occur in the neighborhood of these industries.

Both inorganic and organic forms of selenium are readily absorbed from the gastrointestinal tract of animals. Selenite and selenate are distributed largely to the liver, kidneys, muscle mass, gastrointestinal tract, and blood. The principal route of excertion of selenium is in the urine, mainly as trimethyl selenonium ion.

Most indications of the health effects of selenium are derived from animal studies; the number of reports of industrial or accidental exposures to toxic levels is limited. The severity of response depends on the chemical form of selenium, hydrogen selenide being most toxic. Symptoms of selenium toxicity in animals include gastroenteritis, myocardial damage, hydrothorax, pulmonary edema, and renal and liver damage.

Sodium selenite is toxic to rats at concentrations of 6 to 9 mg/liter in drinking water; concentrations less than 1 mg/liter are without observed toxic effect.

Cited evidence for carcinogenic effects of selenium is tenuous because of poor experimental design or protocol, and has not been confirmed in properly conducted studies. Epidemiological and demographic studies tend to suggest a protective effect of selenium against certain types of cancers, as do statistical data comparing sheep on selenium-supplemented diets with those on normal diets. Tehre are no reports of mutagenicity of selenium.

Although the WHO limit on selenium, like the EPA-proposed maximum contaminant level, is 10 μg/liter and the U.S.S.R. limit is 1 μg/liter as SeO_3, most evidence indicates that there is greater overall potential for selenium deficiency than for selenium toxicity at current levels of selenium intake. The maximum no-observed-adverse-health-effect level for selenium in water is at least 100 μg/liter and apears to be as great as 500 μg/liter. A concentration of 20 μg/liter just barely provides a minimum nutritional amount of selenium with a consumption of 2 liters/day.

A research program should include:

1. Development of more rapid, accurate and reproducible analytical methods of provide qualitative and quantitative assays of chemical forms, oxidation state, and solubility of water.

2. Improved systems for monitoring selenium in the environment (water, air, food).

3. Molecular transformations of selenium compounds in mammalian systems.

4. Interactions between selenium, mercury, cadmium, arsenic, and other trace elements and heavy metals in the biosphere and in animal organisms.

5. Determination of natural and industrial emissions and cycling of selenium in the environment.

6. Effects on animal systems of long-term low levels of selenium, alone and in combination with other trace elements.

7. Baseline data on selenium levels in humans in health and disease.

8. Effects of deficiency or excess of selenium on the development of animal tumors.

9. Studies of the variation in human nutritional requirements for selenium.

Fluoride. Fluoride is found widely in water supplies, but the concentration is usually not great enough to be undesirable. The maximum concentration found for the 969 supplies studied in the 1969 Community Water Supply Survey was 4.4 mg/liter. Most supplies that were not intentionally fluoridated had fluoride concentrations less than 0.3 mg/liter.

A more extensive survey by the Dental Health Division of the U.S. Public Health Service showed that more than 2,600 communities with a population of 8 million people have water supplies with more than 0.7 mg/liter of naturally occurring fluoride. Most of these communities are in Arizona, Colorado, Illinois, Iowa, New Mexico, Ohio, Oklahoma, South Dakota, and Texas. Of these, 524 communities representing 1 million people had supplies with fluoride concentrations greater than 2 mg/liter.

Small amounts of fluoride, on the order of 1 mg/liter, depending on the environmental temperature, in ingested water and beverages, are generally conceded to have a beneficial effect on the rate of occurrence of dental caries, particularly among children.

Two forms of chronic toxic effects are recognized generally as being caused by excess in intake of fluoride over long periods of time. These are mottling of tooth enamel or dental fluorosis, and skeletal fluorosis. In both cases, it is necessary to consider the severity since the very mild forms are considered beneficial by some. The most sensitive of these effects is the mottling of tooth

enamel, which, depending on the temperature, may occur to an objectionable degree with fluoride concentrations in drinking water of only 1.5–2 mg/liter. These observations were made a number of years ago and there have been no recent studies to determine if these levels still cause mottling. Apparently there has been little systematic investigation of the degree to which consumers of drinking water with several mg/liter of fluoride regard the resultant mottling as an adverse health effect.

Skeletal fluorosis has been observed with use of water containing more than 3 mg/liter. It now appears that some probability of objectionable dental mottling exists with and increased bone density long-term consumption of water containing fluoride in excess fo 1 mg/liter in patients with long-standing renal disease and polydipsia. Increased bone density, however, has often been regarded as a beneficial rather than an adverse effect. This therefore makes the implications of such changes unclear. Intake of fluoride for long periods in amounts greater than 20–40 mg/day may result in crippling skeletal fluorosis.

Other reported adverse health effects of intake of milligram per liter levels of fluoride in drinking water, including mongolism, cancer mortality, mutagenic or birth effects and sensitivity have either been unconfirmed or found lacking in substance. There is also no evidence that there is any difference between the effects of naturally occurring or intentionally added fluoride.

Epidemiological studies where the water is naturally high in fluoride have shown no adverse effects other than dental mottling except in rare cases. Controlled studies with fluoridation at the 1 mg/liter level have reported no instances of adverse effects. Available evidence does not suggest that fluoridation has increased or decreased cancer mortality rates.

Additional studies of mottling and skeletal fluorosis need to be done in communities with several mg/liter fluoride in their water supplies to ascertain whether the no-adverse-health effect level for fluoride is greater or less than 1 mg/liter. In addition sociological studies are needed to ascertain the extent to which dental mottling is regarded as an adverse effect.

Nitrate. All sources of combined nitrogen must be regarded as potential sources of nitrate, for there is a tendency for all nitrogenous materials in natural waters to be converted into nitrate. Major point sources of combined nitrogen in water are municipal and industrial wastewaters, refuse dumps, animal feed lots and septic tanks. Diffuse sources include runoff or leachate from manured or fertilized agricultural lands, urban drainage and biochemical nitrogen fixation. Small amounts of combined nitrogen occur in rainfall from solution of atmospheric ammonia and oxides of nitrogen.

In the Community Water Supply survey of the Bureau of Water Hygiene in 1969, the range of nitrate concentrations found was 0–127 mg/liter. Nineteen systems, about 3 percent of those examined for nitrate, had concentrations in excess of the recommended limit of 45 mg/liter.

Ordinarily, the major human intake of nitrate is from food rather than from water. The mean food intake in the United States has been estimated to be nearly 100 mg/day, most of it coming from vegetables such as spinach, lettuce, and root vegetables, which may contain several thousand mg/kg of nitrate.

Nitrate is secreted in the saliva, the mean value being about 40 mg/day, of which about 10 mg/day is reduced to nitrite and found in that form. These quantities, although internally derived, also represent inputs to the gastric system.

Two health hazards are related to the consumption of water containing large concentrations of nitrate (or nitrite): induction of methemoglobinemia, particularly in infants, and possible formation of nitrosamines, some of which may be carcinogenic.

Acute toxicity of nitrate occurs as a result of reduction to nitrite, a process that can occur under specific conditions in the stomach, as well as in the saliva. Nitrite acts in the blood to oxidize hemoglobin to methemoglobin, which does not perform as an oxygen carrier. Consequently, anoxia and death may ensue.

Health adults are reported to be able to consume large quantities of nitrate in drinking water with relatively few effects, if any. Acute nitrate toxicity is almost always seen in infants rather than adults. This increased susceptibility of infants has been attributed to high intake per unit weight, to the presence of nitrate-reducing bacteria in the upper gastrointestinal tract, to the condition of the mucosa, and to greater ease of oxidation of fetal hemoglobin.

Assessment of maximum nitrate levels in water exhibiting no adverse health effects has been based principally on a study of known cases of methemoglobinemia. No cases of methemoglobinemia were found in the original studies in which the water contained less than 10 mg/liter nitrate as nitrogen. Later, a small fraction of total cases was found in which the nitrate concentration of the drinking water was somewhat less than 10 mg/liter as nitrogen. Only one case in the United States has been associated with a public water supply regardless of nitrate content.

Studies supplementary to the previous ones, in which levels of methemoglobin in the blood of infants were related to concentrations of nitrate in the water being fed, showed elevation of methemoglobin levels in infants supplied with water containing nitrate as nitrogen only slightly in excess of 10 mg/liter.

It can be concluded that, from the viewpoint of induction of methemoglobinemia, the maximum concentration of nitrate in water exhibiting no significant adverse health effects is close to the interim standard of 10 mg/liter as nitrogen. However, there appears to be little margin of safety for some infants with the standard at this concentration.

The other health hazard proposed for nitrate in water, that it may act as a procarcinogen, is more speculative. A series of reactions is involved by which it is proposed that nitrate in water may be converted to N-nitroso compounds that may be carinogenic. The steps in the reaction sequence are:

1. Reduction of nitrate to nitrite.
2. Reaction of nitrite with secondary amines or amides in food or water to form N-nitroso compounds.
3. Carcinogenic reaction of N-nitroso compounds.

Reaction of nitrites and secondary amines or amides to form N-nitroso compounds occurs readily in acidic solution, and particularly at the normal pH of 1–5 that is characteristic of gastric contents after a meal.

However, the relation of nitrate concentrations in water supplies to the presence of nitrite in the digestive tract is much more problematic. The major source of nitrite to the stomach, at least for healthy individuals, is the saliva, normally containing 6–15 mg/liter of nitrite. Little reduction of nitrate to nitrite occurs in the human stomach unless the gastric pH is greater than 4.6. Thus the pH for formation of nitrite is quite different from that required for ready formation of N-nitroso compounds, pH 3.5 or less.

Epidemiologically, correlations have been shown between incidence of gastric cancer and concentration of nitrate in the drinking water. An unusually high incidence of stomach cancer in certain mountainous areas of Columbia is associated with high concentration of nitrate in the drinking water. The findings, however, are preliminary and only suggestive. They provide no firm evidence of a causal link between incidence of cancer and high intake of nitrate. They do indicate a need for caution in assessing lack of adverse health effects even at 10 mg/liter nitrate as nitrogen and a need for continued intensive study on the metabolism and effects of nitrate in man.

In conclusion, available evidence on the occurrence of methemoglobinemia in infants tends to confirm a value near 10 mg/liter nitrate as a nitrogen as maximum no-observed-adverse-health-effect level, but there is little margin of safety in this value. There is little scientific basis to support conclusion on the hazard of any concentration of nitrate in water with regard to carcinogenic potential.

Sulfate. No adverse health effects have been noted for concentrations of sulfate in drinking water less than about 500 mg/liter. Diarrhea is the only physiological effect observed at concentrations greater than 1,000 mg/liter.

The taste threshold for sulfate in water lies between 300 and 400 mg/liter for most persons, but some are able to detect as little as 200 mg/liter.

Water hardness and health. A large body of scientific information indicates that certain inorganic or mineral constituents of drinking water are correlated with increased morbidity and mortality rates. These constituents are not usually considered to be "contaminants" since they are often associated with the level of "hardness" of drinking water, and occur naturally or are picked up from water treatment or distribution systems. Hardness is due primarily to the presence of ions of calcium and magnesium and is expressed as the equivalent quantity of calcium carbonate ($CaCO_3$). Water containing less than 75 mg/liter $CaCO_3$ equivalent is generally considered to be soft, and above 75 mg/liter as hard.

The literature suggests that in the United States and other developed nations, the incidence of many chronic diseases, but particularly cardiovascular diseases (heart disease, hypertension, and stroke), is associated with various water characteristics related to hardness. Most of these reports indicate an inverse correlation between the incidence of cardiovascular disease and the amount of hardness. A few reports also indicate a similar inverse correlation between the hardness of water and the risk of several non-cardiovascular causes of death as well.

Several hypotheses have been proposed to account for the correlations; these mostly involve either a protective action attributed to some elements found in hard water or harmful effects attributed to certain metals often found in soft water.

The hypothetically protective agents include calcium, magnesium, vanadium, lithium, chromium, and manganese. The suspected harmful agents include cadmium, lead, copper, and zinc, all of which tend to be found in higher concentrations in soft water as a result of its relative corrosiveness. However, there is disagreement over the magnitude, or even the existence, of a "water factor" in the risk of cardiovascular disease; the identity of the specific casual factors; the mode of action; and the specific pathological effects. The wide spectrum of alleged associated effects, the lack of consistency in

theorized or reported etiologic factors, the very small quantities of the suspected elements in water in comparison with other sources, and the discrepancies between studies, raise serious questions as to whether drinking water serves as a vehicle of casual agents, is an indicator of something broader within the environment, or represents some unexplained spurious associations. Despite these uncertainties, the evidence is sufficiently compelling to treat the "hard water hypothesis" as plausible, particularly when the number of potentially preventable deaths from cardiovascular diseases is considered. In the United States, cardiovascular diseases account for more than one-half of about two million deaths that occur each year. On the assumption that water factors are casually implicated, it is estimated that optimal conditioning of drinking water could reduce this annual cardiovascular disease mortality rate in the United States by as much as 15 percent.

In view of this potential health significance, it is essential to ascertain whether water factors are casually linked to the induction of cardiovascular or other diseases and, if so, to identify the specific factors that are involved. Much more definitive information is needed in order to identify what kinds of remedial water treatment, if any, can be considered.

ORGANIC SOLUTES

The organic compounds that have been identified in drinking water make up a small fraction of the total organic matter present. About 90 percent of the volatile organic compounds have been identified and quantified, but these represent no more than 10 percent by weight of the total organic material. Only 5–10 percent of the non-volatile organic compounds, that comprise the remaining 90 percent of the total organic material, has been identified. (In this context, volatile signifies that the compound is detectable by gas chromatography.)

The compounds selected for review in this study included 74 non-pesticides of the approximately 309 volatile organic compounds so far identified in drinking water, and 55 pesticides. Some of the pesticides studied have not yet been detected in drinking water, but were included because they are or have been used in large quantities. A compound was selected for consideration if any of the following criteria applied:

1. Experimental evidence of toxicity in man or animals, including carcinogenicity, mutagenicity, teratogenicity.

2. Identified in drinking water at relatively high concentration.

3. Molecular structure closely related to that of another compound of known toxicity.

4. Pesticide in heavy use; potential contaminant of drinking water supplies.

5. Listed in the Safe Drinking Water Act or National Interim Primary Drinking Water Regulations.

Toxicological information about the compounds of interest was variable in quality and quantity and, in some instances, inadequate for a proper assessment of toxicity. In evaluating the potential effects on health of these organic compounds the principal concern was to assess their carcinogenicity. At the concentrations found in drinking water, none of the compounds would be expected to produce acute toxicity, but the effects of long continued ingestion of the carcinogens might well become a serious public health problem.

The risk associated with ingestion of compounds that were identified as carcinogenic (to man or animals, confirmed or suspected) were calculated, to the extent that data were available, by the method described in the section on Safety and Extrapolation. The results of these assessments are given in Table 1.

Chronic toxicity of the compounds that were judged not be carcinogenic was assessed by calculating, from such experimental results as were available, Acceptable Daily Intakes (ADI). These values are given in Table 2, together with estimates of maximal no-observed-adverse-health-effect concentrations in water that were derived from them. Compounds that could not be assessed for lack of experimental evidence are listed in Tables 3 and 4.

The ADI [1] represents an empirically derived value that reflects a particular combination of both knowledge and uncertainty concerning the relative safety of a chemical. When there is more confidence about data derived from animal experiments or observations on humans the uncertainty factor is smaller than when little is known about the potential toxicity of a chemical. These numbers are not meant to represent a guaranteed safety level, but rather to indicate a level at which exposure to the single chemical in question is not anticipated to produce an observable toxic response in man. The ADI values do not consider interactions (e.g. synergism, antagonism) among the many possible contaminants. Furthermore the ADI values do not represent safe levels in drinking water, because they do not take into account what fraction of the potential contaminant intake may come from water.

Suggested no-observed-adverse-health-effects concentrations in water have been calculated under two different assumptions: (1) That 20 percent of total intake of a material is from water and 80 percent from other sources, and (2) that 1 percent of total intake is from water and 99 percent from other sources (See Table 2). Similar calculations can be made for other materials discussed in this report using such data as may be available with regard to concentration of the contaminant in food or other sources.

Because the experimental data on the effects of many substances are inconsistent, "no-observed-adverse health effect" levels cannot be firmly specified for all organic contaminants. Most of the materials considered have not been studied sufficiently to firmly establish their carcinogenic potential with certainty. The risk assessments do not take into account interactions such as additive toxicity, synergism, and antagonism. What ultimately may be most important is the interaction of these compounds with each other and with other material in contributing to the total body burden resulting from multiple sources of contaminant exposure. For these reasons the ADI is intended to be used only as a guide for assessment of toxicity from chronic exposure. Furthermore, an ADI is not meant to provide a basis for the continuing discharge of a compound into the environment.

In the present limited state of our knowledge concerning structure-activity relationships for carcinogenic and other toxic effects, one cannot consistently and accurately extrapolate these properties from one compound to another. Nevertheless, in certain instances (for example, the substitution of bromine for chlorine in a halogenated methane) it is presumed that the relationship is sufficiently strong to justify the suspicion that the related compounds may be similarly toxic.

[1] The Committee considered several alternative terms, other than ADI, but concluded that the introduction of a substitute for ADI might well lead to confusion. The term "Acceptable Daily Intake" is used throughout the discussion because of its adoption by international organizations.

The potential for existing concentrations of organic pesticides and other organic contaminants in drinking water to adversely affect health, cannot be answered with certainty at this time. The key issue is whether or not certain organic chemicals found in very low concentrations can cause or increase the rate of cancer development in man. Even though several of these chemicals have demonstrated carcinogenicity in laboratory animals, the extrapolation of such results to man remains difficult for a number of reasons.

Because of bioassays that have been used to establish carcinogenicity of certain organic chemicals are conducted at doses which are hundreds to thousands of times greater than the levels at which these chemicals occur in water, the risks at these low levels must be obtained by extrapolation from higher doses. There is no hard evidence that low level oral exposure to any of these chemicals produces cancer. An argument has been made that the dose levels used to establish carcinogenicity are so high that they overwhelm normal detoxification or repair mechanisms or both, and produce cancer by some mechanism that does not operate under low dose conditions. Experimental animals subjected to such high doses could be considered a population different from those exposed to lower doses that do not produce pathological alterations and changes in pharmacokinetic parameters, or biochemistry.

Extrapolating from laboratory animals to man would be more meaningful if comparative metabolic information between the different species were available. Some species do not metabolize a parent compound to its activated form so that use of these species in toxicological bioassays is inappropriate if the compound undergoes activation in man. The converse situation also is true. Difference may also occur with respect to other parameters such as rates of biotransformation, absorption, excretion, and biological half life.

Risk assessments based on extrapolations which fail to consider species differences with respect to sensitivity, tissue susceptibility, kinetics, pathology or biotransformation pathways may be inappropriate. This kind of information is not presently available.

In light of such uncertainties, a cautious approach must be adopted when dealing with potentially harmful chemicals. Even more uncertainty exists when one considers the possibility that some of these chemicals may also be mutagenic or teratogenic. The methodologies used to establish these effects are even less applicable to man than cancer bioassays.

For many of the organic compounds identified in drinking water, virtually no toxicity data are available. Ideally, all of these agents (as well as any new ones) should be subjected to an extensive battery of toxicity tests including chronic bioassay. In practice, there is a need to determine those agents for which the generation of data is most pressing. Several criteria are important for the development of an order of priority for testing.

The main factors identified in the assignment of priorities are:

1. The relative concentrations of the compounds and the number of people likely to be exposed as well as the identity of defined subpopulations exposed,

2. The number of water systems in which they occur,

3. Positive responses to in vitro mutagenic screening systems,

4. Positive responses to in vitro carcinogen pre-screens (mammalian cell transformations),

5. Similarity of chemical structure of the test compound to those of other compounds

having defined toxic properties (i.e. structure-activity relationships) and

6. Relationship of dose from water to total body burden.

A number of assays using bacteria and yeast have shown promise in yielding high correlations between mutagenic activity and known carcinogenic activity for certain classes of materials. These may prove to be useful in establishing a first level screen for potential carcinogens.

CONCLUSIONS

Carcinogenicity. Table 1 lists the organic contaminants for which positive data on carcinogenesis exist. For these compounds, where adequate (lifetime) feeding studies were available, a statistical extrapolation of risk was performed. The method is described in the section on Safety and Extrapolation. The numbers in Table 1 are upper 95 percent confidence estimates of cancer risk to man from a lifetime of exposure to a particular compound. These estimates have been corrected for interspecific differences (that is, between the experimental animal and man on the basis of relative surface area.

Bacterial Mutagenicity. In addition to examining data from animal feeding studies for the identification of suspect carcinogens, data for mutagenesis in bacteria, or other test systems were also examined. Available data are summarized as follows: (1) Benzo(a)pyrene, chlorodibromomethane, Captan, and Folpet have been found to be mutagenic; (2) Bromoform and vinyl chloride, weakly mutagenic; (3) Carbon tetrachloride, bromobenzene, nicotine, DDE, dieldrin, carbaryl and trifluraline, non-mutagenic.

Teratogenicity. Data on teratogenic potential exist for 24 of the compounds under study. Hexachlorophene, nicotine, the phthalate esters, 2,4-D, 2,4,5-T, and Folpet have been shown to be teratogens, while benzene, benzo(a)pyrene, carbon tetrachloride, PCB's, Captan, Carbaryl, Chlordan, DDT, Kepone, Malathion, Methylparathion, Mirex, Paraquat, and Parathion have been reported to be non-teratogenic. Nowhere is the paucity of toxicologic data more evident than in the data on teratogenesis.

Non-Carcinogenic Toxicity. For 45 compounds there were sufficient data to calculate ADI's. These are summarized in Table 2. Occasionally the ADI was calculated from partial lifetime exposure studies when no other data were available. Toxicity was measured by various responses.

The health effects of many compounds of interest could not be assessed because toxicological information about them was inadequate or unavailable. These compounds are listed in Tables 3 and 4, together with their reported occurrence in drinking water in the United States.

TABLE 1.—*Categories of known or suspected organic chemical carcinogens found in drinking water*

Compound	Highest observed concentrations in finished water (microgram per liter)	Upper 95 pct confidence estimate of lifetime cancer risk per (microgram per liter) [1]
Human carcinogen: vinyl chloride	10	5.1×10^{-4}
Suspected human carcinogens:		
Benzene	10	[4]
Benzo(a)pyrene	[2]	[4]
Animal carcinogens:		
Dieldrin	8	2.6×10^{-4}
Kepone	[2]	4.4×10^{-4}
Heptachlor	[2]	4.8×10^{-4}
Chlordane	.1	1.8×10^{-4}
DDT	[2]	1.2×10^{-4}
Lindane (γ-BHC)	.01	9.3×10^{-4}
α-BHC	[2]	6.5×10^{-4}
β-BHC	[2]	4.2×10^{-4}
PCB (Arocior 1260)	3	3.1×10^{-4}
ETU	[2]	2.2×10^{-4}
Chloroform	366	3.7×10^{-7}
Carbontetrachloride	5	1.5×10^{-7}
PCNB	[2]	1.4×10^{-4}
Trichloroethylene	.3	1.3×10^{-7}
Diphenylhydrazine	1	[4]
Aldrin	[2]	[4]
Suspected animal carcinogens:		
Bis(2-chloroethyl)-ether	.42	1.2×10^{-4}
Endrin	.08	[4]
Heptachlor epoxide	[2]	[4]

[1] See text for details.
[2] Detected but not quantified.
[3] Not detected.
[4] Insufficient data to permit a statistical extrapolation of risk.

TABLE 2.—*Organic pesticides and other organic contaminants in drinking water, concentration, toxicity, ADI and suggested no adverse effect levels*

Compound	Maximum observed concentrations in water (microgram per liter)	Maximum dose producing no observed adverse effect (milligram per kilogram per day)	Uncertainty factor [1]	ADI [2] (milligram per kilogram per day)	Suggested no adverse effect level from water, microgram per liter assumptions [3]	
					1	2
2,4-D	0.04	12.5	1,000	0.0125	87.5	4.4
2,4,5-T		10.0	100	.1	700	35
TCDD		10^{-6}	100	10^{-7}	7×10^{-4}	3.5×10^{-6}
2,4,5-TP	[4]	.75	1,000	.00075	5.25	.26
MCPA		1.25	1,000	.00125	8.75	.44
Amiben		250	1,000	.25	1750	87.5
Dicamba		1.25	1,000	.001125	8.75	.44
Alachlor	2.9	100	1,000	.1	700	35
Butachlor	.06	10	1,000	.01	70	3.5
Propachlor		100	1,000	.1	700	35
Propanil		20	1,000	.02	140	7
Aldicarb		1	100	.001	7	.35
Bromacil		12.5	1,000	.0125	87.5	4.4
Paraquat		8.5	1,000	.0085	59.5	2.98
Trifluralin (also for Nitralin and Benefin)	[4]	10	100	.1	700	35
Methoxychlor		10	100	.1	700	35
Toxaphen		1.25	1,000	.00125	8.75	.44
Azinphosmethyl		.125	10	.0125	87.5	4.4
Diazinon		.02	10	.002	14	.7
Phorate (also for Disulfoton)		.01	100	.0001	.7	.035
Carbaryl		8.2	100	.082	574	28.7
Ziram (and ferbam)		12.5	1,000	.0125	87.5	
Captan		50	1,000	.05	350	17.5
Folpet		160	1,000	.16	1,120	56
HCB	6	1	1,000	.001	7	.35
PDB	1	13.4	1,000	.0134	93.8	4.7

Compound	Maximum observed concentrations in water (microgram per liter)	Maximum dose producing no observed adverse effect (milligram per kilogram per day)	Uncertainty factor [1]	ADI [2] (milligram per kilogram per day)	Suggested no adverse effect level from water, microgram per liter assumptions [3]	
					1	2
Parathion (and methyl parathion)		.043	10	.0043	30	1.5
Malathion		.2	10	.02	140	7
Maneb (and zineb)		.5	1,000	.005	35	1.75
Thiram		5	1,000	.005	35	1.75
Atrazine	5.0	21.5	1,000	.0215	150	7.5
Propazine	(4)	46.4	1,000	.0464	325	16
Simazine	(5)	215	1,000	.215	1505	75.25
Di-n-butyl phthalate	5	110	1,000	.11	770	38.5
Di (2-ethyl hexyl) phthalate	30	60	100	.6	4,200	210
Hexachlorophene	.01	1	1,000	.001	7	.35
Methyl methacrylate	1	100	1,000	.1	700	35
Pentachlorophenal	1.4	3	1,000	.003	21	1.05
Styrene	1	133	1,000	.133	931	46.5

[1] Uncertainty factor—the factor of 10 was used where good chronic human exposure data was available and supported by chronic oral toxicity data in other species, the factor of 100 was used where good chronic oral toxicity data were available in some animal species, and the factor of 1,000 was used with limited chronic toxicity data or when the only data available were from inhalation studies.

[2] Acceptable daily intake (ADI)—maximum dose producing no observed adverse effect divided by the uncertainty factor.

[3] Assumptions: Average weight of human adult = 70 kg. Average daily intake of water for man = 2 liters.
1. 20 pct of total ADI assigned to water, 80 pct from other sources.
2. 1 pct of total ADI assigned to water, 99 pct from other sources.

[4] Detected but not quantified.

[5] Detected.

TABLE 3.—*Organic pesticides and other organic contaminants found in drinking water, with insufficient data on chronic toxicity*

	Highest concentration in finished water (microgram per liter)
Acetaldehyde	0.1
Acrolein	
Bromobenzene	(1)
Bromoform	(1)
Carbon disulfide	(1)
Chloral	5.0
Chlorobenzene	5.6
Cyanogen chloride	.1
1,2-Dichloroethane	21.0
2,4-Dichlorophenol	36.0
2,4-Dimethylphenol	(1)
e-Caprolactam	(1)
Hexachloroethane	4.4
O-Methoxyphenol	(1)
Methyl chloride	(1)
Methylene chloride	7.0
Phenylacetic acid	4.0
Phthalic anhydride	(1)
Propylbenzene	<5.0
t-Butyl alcohol	.01
Tetrachloroethane	4.0
Tetrachloroethylene	<5.0
Toluene	11.0
Trichlorobenzene	1.0
1,1,2-Trichloroethane	(1)
Nicotine	3.0
Methomyl	
Cyanazine	(1)
xylene	<5.0

[1] Detected but not quantified.

TABLE 4.—*Organic contaminants found in drinking water; information on chronic toxicity lacking*

Compound	Highest concentration in finished water (microgram per liter)	Highest concentration in raw water (microgram per liter)
1,2-Bis (chloroethoxy) ethane	0.03	
Bis(2-chloroisopropyl) ether	1.58	
Bromochlorobenzenes	(1)	
Bromodichloromethane	116	11
Butyl bromide	(1)	
Chloroethyl methyl ether	(1)	
Chlorodibromomethane	100	1.4
Chlorohydroxybenzophenone	(1)	
Chloromethyl ethyl ether	(1)	
Chloropropene	(1)	
Crotonaldehyde	5.0	
Dibromobenzene	(1)	
Dibromodichloroethane	0.63	
1,3-Dichlorobenzene	<3.0	
Dichlorodifluoroethane	(1)	
Dichlorofodomethane	0.5	
1,1-Dichloro-2-hexano	1.0	
1,2-Dichloropropane	<1.0	
1,3-Dichloropropene	<1.0	
1,2-Dimethoxybenzene	(1)	
4,6-Dinitro-2-aminophenol	(1)	
Dioctyladipate	20.0	
Hexachloro-1,3-butadiene	0.07	
Isodecane	5.0	
Metachloronitrobenzene	(1)	
Methylstearate	(1)	
Nonane	4.0	
Octyl chloride	(1)	
Pentachlorophenyl methyl ether	0.1	
1,1,3,3-Tetrachloroacetone	1.0	1.0
2,4,6-Trichlorophenol	(1)	
Trimethylbenzene	6.1	

[1] Detected.

RESEARCH RECOMMENDATIONS

1. Because great uncertainty exists in connection with extrapolation of data from the present cancer bioassays, better premises and methodologies are needed to establish the extent to which humans are at risk from the low level exposures to organic substances in water. There is a need to know the extent to which low level exposure to a presumed carcinogen does in fact increase the probability of cancer during the lifetime of an individual.

It is recommended that work be done to better characterize current animal models and also develop new ones. Studies on the comparative metabolism between laboratory animals and man are urgently needed. It is necessary to know, for example, if a laboratory animal metabolizes a test compound in the same manner and rate as man. Better mutagenicity bioassays using mammalian cells should be developed. More work is needed in the area of interactions and synergism which these assay systems could more easily accommodate.

2. Organic material in water is thought by many to be responsible for contributing the initial reactants for many potentially harmful contaminants. To this end total organic carbon (TOC) in drinking water supplies must be better characterized and more extensively determined. Because some halogenated compounds are formed by chlorination of naturally occurring organic substances research on methods for destruction or removal of organic precursors of halogenated compounds prior to chlorination would lead to reduction in chlorinated products and their accompanying health hazards.

3. Epidemiologic studies to obtain quantitative measures of association between the frequency of malignant disease in humans and exposure to specific organic compounds found in drinking water are needed. In particular, ways are needed to develop useful epidemiologic data from examination of small populations of individuals occupationally exposed to drinking water contaminants. A major effort now needs to be directed at determining the health status of workers in industries where there is occupational exposure to compounds identified as animal carcinogens.

More accurate record keeping, a national death index, and more reliable analytical methods to monitor environmental exposure are needed.

4. There is a need for more and better toxicological data, on compounds which could not be evaluated at this time, especially creosote, methyl parathion, and acrolein all of which are high use pesticides. Data are needed in the area of low level, chronic (life time) exposures. Studies should include exposure to formulated products (i.e. mixtures) as well as pure compound.

5. There should be a periodic re-evaluation by newer, more sensitive and more predictive methodologies of these pesticides used in large volume.

DEFINITIONS

The Safe Drinking Water Committee adopted the following working definitions prior to its review of the scientific literature of organic contaminants:

Carcinogen. The term carginogen is used in its broad sense, because in most of the current human epidemiologic approaches and certain animal bioassays it is not possible to differentiate clearly between initi-

ating agents, promoting agents, and certain modifying factors. Any factor or combination of factors which increases the risk of cancer in humans is of concern regardless of its mechanism of action. The criteria listed here apply only to chemical agents.

A malignant neoplasm is composed of a population of cells displaying progressive growth and varying degrees of autonomy and cellular atypia. It displays, or it has the capacity for, invasion of normal tissues, metastases, and causing death to the host. Benign neoplasms are a less autonomous population of cells and exhibit little or no cellular atypia or invasion of normal tissues and do not metastasize. In particular cases, however, benign neoplasms may endanger the life of the host by a variety of mechanisms, including hemorrhage, encroachment on a vital organ, or unregulated hormone production. The cytologic and histologic criteria utilized in determining whether a lesion is benign or malignant differ depending upon the tissue in which the neoplasm arises. Evaluation of whether a specific lesion is benign or malignant should therefore, follow standard criteria used by experimental oncologists and pathologists with the emphasis on correlation of the histopathologic pattern with the biologic behavior of the lesion or type of lesion. In equivocal cases, the diagnosis of a specific lesion may require a panel of experts; recognizing that they may not always agree.

Depending upon the particular case, benign neoplasms may represent a stage in the evolution of a malignant neoplasm and in other cases they may be "end points" which do not readily undergo transition to malignant neoplasms.

A. CRITERIA IN HUMAN STUDIES

An agent—which may comprise a combination of chemicals—is carcinogenic in man if it increases the incidence of malignant neoplasms (or a combination of benign and malignant neoplasms) in humans to levels that are significantly higher than those in a comparable group not exposed (or exposed at a lower dose) to the same agent. If all of the induced neoplasms are benign, rather than malignant, then, for the reasons given elsewhere in this document, the agent must be considered a possible carcinogen and it should, therefore, be very carefully evaluated as a health hazard.

Types of evidence suggesting that an agent is carcinogenic in humans include: Neoplastic response directly related to exposure (both duration and dose); incidence and mortality differences related to occupational exposure; incidence and mortality differences between geographic regions related to different exposures rather than genetic differences and/or altered incidence in migrant populations; time trends in incidence or mortality related to either the introduction or removal of a specific agent from the environment; case control studies; and the results of retrospective-prospective and prospective studies of the consequences of human exposure. Clinical case reports may also provide early warning of a potential carcinogen. Negative epidemiologic data may not establish the safety of suspected materials. Negative data on a given agent obtained from extensive epidemiologic studies of sufficient duration are useful for indicating upper limits for the rate at which a specific type of exposure to that agent could affect the incidence and/or mortality of specific human cancers.

B. CRITERIA IN EXPERIMENTAL ANIMAL STUDIES

The carcinogenicity of a substance is established when the administration to groups of animals in adequately designed and conducted experiments results in increases in the incidence of one or more types of malignant neoplasms (or a combination of benign and malignant neoplasms) in the treated groups as compared to control groups maintained under identical conditions but not given the test compound. The increased incidence of neoplasms in one or more of the experimental groups should be evaluated statistically for significance, and the only major experimental variable between the control and the experimental group should be the absence or presence of the single test agent. Such increases may be regarded with greater confidence if positive results are observed in more than one group of animals or in different laboratories. The demonstration that the occurrence of neoplasms follows a dose-dependent relationship provides additional evidence of a positive result.

The occurrence of benign neoplasms raises the strong possibility that the agent in question is also carcinogenic since compounds that induce benign neoplasms frequently induce malignant neoplasms. In addition, benign neoplasms may be an early stage in a multi-step carcinogenic process and they may progress to malignant neoplasms; also, benign neoplasms may be an early stage in the health and life of the host. For these reasons, if a substance is found to induce benign neoplasms in experimental animals it should be considered a potential human health hazard which requires further evaluation. In experiments where the increased incidence of malignant neoplasms in the treated group is of questionable significance, a parallel increase in incidence of benign tumors in the same tissue adds weight to the evidence for carcinogenicity of the test substance (from General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances. Report of the Subcommittee on Environmental Carcinogenesis NCI, 1976).

Mutagen. A chemical that is capable of producing a heritable change in genetic material. These changes may be either point mutations or chromosomal mutations and can occur in either somatic or germ cells.

Teratogen. An agent which acts during pregnancy to produce a physical or functional defect in the developing offspring.

Organoleptic test. The use of odor and taste thresholds to establish permissible levels of exposure to chemicals.

Adverse Response. "With increasing dosage in the continuum of the dose-response relationship, the region is generally entered where the effects are clearly adverse. Thus, adverse effects may be defined as changes that:

1. Occur with intermittent or continued exposure and that result in impairment of functional capacity (as determined by anatomical, physiological, and biochemical, or behavioral parameters) or in a decrement of the ability to compensate for additional stress;

2. Are irreversible during exposure or following cessation of exposure if such changes cause detectable decrements in the ability organism to maintain homeostasis; and

3. Enhance the susceptibility of the organisms to the deleterious effects of other environmental influences."

(From the NAS publication, Principles for Evaluating Chemicals in the Environment, 1975)

Toxicity. The intrinsic quality of a chemical to produce an adverse effect. The term includes capacity to induce teratogenic, mutagenic, and carcinogenic effects.

Safety. "Safety is the practical certainty that injury will not result from the substance when used in the quantity and in the manner proposed for its use."

(From Evaluating the Safety of Food Chemicals, NAS, 1970)

Evaluation of Safety. "An estimation of the potential of the substance to cause injury and review and evaluation of sufficient data to warrant a conclusion that the conditions of proposed use will provide an intake so low in relation to the toxic dose that there is a practical certainty no harm can result." (from FDA Papers, November, 1971)

For the purpose of this study the proposed use was limited only to exposure from drinking water.

Safety Factor or Uncertainty Factor. A number that reflects the degree or amount of uncertainty which must be considered when experimental data in animals are extrapolated to man. When the quality and quantity of data are high the uncertainty factor is low and when data are inadequate or equivocal, the uncertainty factor must be larger.

The following general guidelines have been adopted in establishing the uncertainty factors.

1. Valid experimental results from studies on prolonged ingestion by man, with no indication of carcinogenicity. Uncertainty Factor = 10

2. Experimental results of studies of human ingestion not available or scanty (e.g., acute exposure only). Valid results of long-term feeding studies on experimental animals or in the absence of human studies, valid animal studies on one or more species. No indication of carcinogenicity. Uncertainty Factor = 100

3. No long-term or acute human data. Scanty results on experimental animals. No indication of carcinogenicity. Uncertainty Factor = 1,000

These uncertainty factors are used in every case as a divisor of the highest reported long-term dose that is observed not to produce any adverse effect.

CARCINOGENS: CATEGORIES IN TABLE 1.

Human Carcinogen—Based on strong epidemiological evidence and toxicological studies in animals.

Suspected Human Carcinogens—Based on limited epidemiological evidence in man and equivocal toxicological studies in animals.

Animal Carcinogens—Based on toxicological studies in at least one species of animal.

Suspected Animal Carcinogens—Based on equivocal toxicological studies in animals or on a structural similarity to a known carcinogen.

RADIOACTIVITY IN DRINKING WATER

Everyone is exposed to some natural radiation that comes from both cosmic rays and terrestrial sources. Although there are large geographic variations in the amount of natural background radiation, the average background dose in the United States is about 100 mrem/year. A small proportion of this unavoidable background radiation comes from drinking water that contains radionuclides.

By far the largest contribution to the radioactivity in drinking water comes from potassium-40, which is present as a constant percentage of total potassium. Only a small percentage of the total potassium-40 body burden, however, comes from drinking water. The total body dose from other possible radioactive contaminants of water constitutes a small percentage of the background radiation to which the population is exposed. Although the amounts of individual radioactive contaminants fluctuate from place to place, calculations made for a hypothetical water supply that might be typical for the United States have shown that a total soft-tissue dose of only 0.24 mrem/year would be contributed by all the radionuclides found in the water. Even with rather wide fluctuations in the concentrations, the total contribution of the radionuclides will remain very small.

However, bone-seeking radionuclides—such as strontium-90, radium-226, and radium-228—account for a somewhat larger propor-

tion of the total bone dose. This is particularly true for the two isotopes of radium because they emit high-linear-energy-transfer (LET) radiation, and because certain restricted localities have been found to have rather high concentrations of radium in drinking water. Nevertheless, in the hypothetcal typical water supply, less than 10 percent of the annual background dose comes from such radiation. It has also been estimated that the total population exposed to levels of radium greater than 3 pCi/liter is about a million people. About 120,000 people are exposed to radium at levels greater than 9 pCi/liter.

Risk estimates were made of three kinds of adverse health effects that radiation could produce: developmental and teratogenic effects, genetic effects, and somatic (chiefly carcinogenic) effects.

DEVELOPMENTAL AND TERATOGENIC EFFECTS

The developing fetus is exposed to radiation from radionuclides in drinking water for nine months. Thus, the total dose accumulated by the fetus will be very small. Furthermore, although the fetus is sensitive to the effects of radiation in some stages of development, these periods are sharply limited and extremely short. For this reason, too, the total dose administered that could have possible developmental and teratogenic effects would be extremely small. Current concentrations of radionuclides in drinking water lead to doses of about one five-thousandth of the lowest dose at which a developmental effect has been found in animals. Therefore, the developmental and teratogenic effects of radionuclides would not be measurable.

GENETIC EFFECTS

It has been estimated that there are about 94,400 genetic diseases per million live births in the United States. The maximum permissible dose of man-made radiation for the general population (170 mrem/year) has been estimated to increase this number in the first generation by 170–215, with an unlikely upper limit of 4,250. On the basis of a 30-year generation and 3.6 million live births per year in the United States, we would expect the 0.24 mrem soft-tissue dose, or gonad dose, to lead to 0.0098 additional cases of genetic disease per million live births per year or 0.035 additional cases of genetic disease in the United States per year. Even at the unlikely extreme upper limit of possible genetic effects of radiation of around 4,000 extra cases in the first generation, there would still be less than one additional case in the $94{,}400 \times 3.6 = 340{,}000$ live births with genetic defects. The wide fluctuation in bone dose caused by fluctuations in the radium concentration of drinking water would not have any sensible effect on the genetically significant dose, because radium is predominantly a bone-seeker and will deliver very little radiation to the gonads.

SOMATIC AND CARCINOGENIC EFFECTS

The natural background of radiation can be estimated to cause 4.5 to 45 cases of cancer per million people, depending on the risk model used. The amount of whole-body radiation from radionuclides in typical drinking water contributes less than 1 percent of this amount, and thus, for cancers other than those in bone, may cause a negligible increase in the total. Radium, however, can contribute somewhat less than 7 percent of the total bone dose received from background radiation in areas of "normal" radium concentration. The average carcinogenic risk associated with skeletal irradiation by radium in a population with a typical distribution of ages, is estimated to approximate 0.2 fatal cases of bone cancer per million persons per year per rem. Therefore, over a period from 10 to 40 years after the beginning of skeletal irradiation, the average risk attributable to natural background radiation is estimated to range from 0.6 per million persons per year, under typical conditions, to as much as 4.2 per million per year, in regions where 25 pCi/liter of radium-226 are found in the drinking water. It has been noted that in the United States 120,000 people are estimated to drink water containing between 9 and 25 pCi/liter or radium-226 and only a small number lie near the upper end of this range. The number of excess cancers in this group would therefore lie between 0.16 and 0.43 per year. Since not all the 120,000 people drink water containing 25 pCi/liter of radium-226, the latter number is inordinately high.

CONCLUSIONS

The radiation associated with most water supplies is such a small proportion of the normal background to which all human beings are exposed, that it is difficult, if not impossible, to measure any adverse health effects with certainty. In a few water supplies, however, radium can reach concentrations that pose a higher risk of bone cancer for the people exposed.

FUTURE NEEDS

The precision of estimation of the health risks associated with radioactivity in drinking water could be enhanced if several water systems were analyzed to determine the complete distributions of beta and alpha radiation that constitute the gross counting measurements.

Because the precise ratio of radium-228 to radium-226 in water has not been measured extensively, an attempt should be made to determine the ratio in several ground and surface waters whose content of radium-226 is known. The waters to be analyzed should range from about 0.1 to 50 pCi/liter. The percentage of the daughter radionuclides present should be determined.

Because radon is a noble gas that is quickly released from water, it is possible that, in some areas of high radon content, water vapor containing radon might constitute an inhalation hazard when such water is used, for example, in humidifiers or for showers. A determination should be made whether or not radon emanations from water do indeed constitute an inhalation hazard.

The models used in this report do not take into account the possibility that the finely divided solid particles that occur in water may alter the uptake of radionuclides. The effects of the solids in drinking water on the metabolism and uptake of radionuclides merit investigation.

[FR Doc.77-19232 Filed 7-8-77;8:45 am]